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The Excretion of 17-Ketosteroids in Patients with Hyperthyroidism and Myxedema[1]

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THE EVIDENCE now available indicates that the urinary 17-ketosteroids are the excretion products of substances produced by the adrenal cortex and the testicles. In women, therefore, the measurement of the 17-ketosteroids is considered to be an index of some phases of the activity of the adrenal cortex alone; in men, it is an index of the combined activities of the adrenal glands and the testicles. The evidence for these conclusions was obtained from studies on eunuchs (1), on normal and castrate women (2, 3), on normal men (4), on patients who had adrenal cortical tumors and those who had adrenal hyperplasia (5–8), on patients who had Addison's disease (8, 9), on a man who had an interstitial cell tumor of the testicle (10) and on hypogonad men receiving testosterone (11, 12). The exact significance of the total urinary 17-ketosteroids or of their individual components cannot be assessed without more fundamental knowledge of their precursors and intermediary metabolism. Nevertheless, the measurement of the quantity excreted during a given period does afford a valuable tool for the study of the hormonal activity of the adrenal cortex and the male gonad. With this thought in mind patients who had hyperthyroidism and others who had myxedema were studied in order to determine the effect of these endocrine disturbances on the function of the glands mentioned.

A few reports are available on the excretion of androgens and 17-ketosteroids by patients who had hyperthyroidism and by others who had myxedema. In a study of three cases of Graves' disease, Baumann and Metzger (13) reported that while these patients were improving during treatment there was a "lowering of the urinary androgens as measured biologically though not when determined colorimetrically." They also stated that "compared to the normal standards, the androgen output in Graves' disease is frequently increased in both men and women."

[1] Abridgment of thesis submitted by Dr. Engstrom to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

This latter observation is in contrast to the studies of Marine and Rosen (14) on ten patients who had Graves' disease. Their patients showed wide variations of excretion of androgens as measured by the capon comb test; some of their patients exhibited normal excretion of androgens but the majority showed a diminished output. However, treatment of these patients with iodine caused a further depression of urinary androgens, particularly if there was clinical evidence of improvement. The significance of this observation is not known and further investigations are indicated. Marine and Rosen also presented data on two cases of untreated myxedema in which the excretion of androgenic substances was very small; the urine of the patients showed a "significant rise" in the amount of capon comb-growth-promoting substances following two and a-half and three months of treatment with desiccated thyroid.

These studies did not include assays of the urinary 17-ketosteroids. However, Friedgood (15), without presenting detailed data, reported that the excretion of 17-ketosteroids was extraordinarily low in ten cases of spontaneous and postoperative myxedema but he found that "adequate thyroid replacement therapy was without significant effect on the level of the 17-ketosteroid excretion."

Fraser and co-workers (8) reported that the excretion of 17-ketosteroids was always low (ranging from 0.6 to 1.8 mg. per twenty-four hours) among six women suffering from untreated hypothyroidism. No data were given concerning the changes that might occur with thyroid therapy. Fraser and co-workers also presented data on three cases of hyperthyroidism in which excretion of 17-ketosteroids was somewhat lowered (ranging from 1.3 mg. to 5.6 mg. per twenty-four hours). They attributed this lowering to "secondary, non-specific factors, rather than to a fundamental action of the [thyroid] hormone."

Talbot and co-workers (16) measured the excretion of 17-ketosteroids by twelve children suffering from hypothyroidism while the children were receiving daily maintenance doses of desiccated thryoid. The "developmental age" of these children was retarded below their chronologic age and their output of 17-ketosteroids tended to be slightly low, even though they were free from the symptoms of myxedema and their basal metabolic rates were normal. No data were given on the level of the excretion of 17-ketosteroids before treatment.

In view of the relative paucity of detailed information regarding the excretion of the urinary 17-ketosteroids by hyperthyroid and myxedematous patients under varied conditions, it was thought worth while to investigate this problem further. Therefore, the excretion of neutral 17-ketosteroids by patients suffering from exophthalmic goiter (Graves' disease) and adenomatous goiter with hyperthyroidism was measured before and during preoperative treatment with iodine. Also, patients who had spontaneous and secondary myxedema were studied with respect to their output of 17-ketosteroids before and during treatment with desiccated thyroid.

METHODS

Collection of samples of urine. Accurately timed[2] twenty-four hour specimens of urine were collected in glass bottles containing 5 cc. of concentrated hydrochloric acid as a preservative. Aliquots of the specimens were either worked up immediately or preserved in the ice box for not longer than three days. The crude extracts were prepared essentially by the method described by Talbot and co-workers (17), using independent hydrolysis and extraction. For the colorimetric assay of the crude extracts the Callow (18) method was employed, with application of the previously described equation (8, 19) to compensate for the presence of chromogens that were not 17-ketosteroids.

Collections were made from fifteen patients who had exophthalmic goiter[3] (Graves' disease) and from seven patients who had adenomatous goiter with hyperthyroidism. The spec-

[2] The patients were sent to the laboratory, where they were given written and verbal directions for the collection of the twenty-four hour specimens of urine. When the bottles were returned to the laboratory, the patients were questioned concerning the accuracy of the collection.

[3] The diagnosis of exophthalmic goiter was based on the clinician's diagnosis of "exophthalmic goiter" and the pathologist's confirmation of a "parenchymatous, hyperplastic" thyroid. The patients were under the care of Drs. S. F. Haines, E. J. Kepler, E. H. Rynearson, R. G. Sprague and F. R. Keating and we appreciate the co-operation of these physicians in making this study possible.

imens were obtained before and during treatment with compound solution of iodine (Lugol's solution[4]). Ten patients who had myxedema were studied before and during treatment with desiccated thyroid. One case of anterior pituitary insufficiency with dwarfism and low basal metabolic rate was included.

RESULTS

Range of normal values. The levels of excretion of urinary 17-ketosteroids for normal men and women were established as standards for comparison with the values found for the patients who had thyroid disease. The average value found for thirteen sexually mature, normal men was 14.2 mg. per twenty-four hours, with a range of 9.8 mg. to 20.8 mg. The average for fifteen sexually mature, normal women was 10.2 mg. per twenty-four hours, with a range of 5.8 mg. to 17.0 mg.[5] Studies in other laboratories with similar methods have given comparable results. Investigations by Bachman and co-workers (20), Forbes and Friedman (21), Werner (22) and Fraser and co-workers (8) have shown that the output during consecutive twenty-four hour periods is not absolutely constant from day to day for the same subject. Talbot and Butler (23) stated that "the fluctuations which occur under normal circumstances are not great; the chances being two to one that a single specimen will fall within 15 per cent of the 17-ketosteroid value obtained by averaging 30 or 40 consecutive daily specimens. . . . It therefore appears that one or two accurately timed and collected twenty-four hour specimens of urine suffice for assay for most clinical diagnostic purposes." Also Talbot and co-workers (16) stated that "in no instance did any value obtained for one subject deviate from the average value by more than ± 30 per cent."

Results obtained before and after treatment with iodine, for patients who had hyperthyroidism. The detailed data in the fifteen cases of exophthalmic goiter (Graves' disease) are given in table 1. The average output of 17-ketosteroids in twenty-four hours of seven women before treatment with iodine was 7.2 mg. This is slightly less than the average of 10.2 mg. for normal women but within the normal range. There was no significant difference in the amount of 17-ketosteroids excreted by those women who had exophthalmos[6] (7.0 mg. in twenty-four hours) and by those who did not have exophthalmos (7.4 mg. in twenty-four hours). The average output of the eight men, before treatment with iodine, was 10.1 mg. per twenty-four hours. This again is slightly less than the average of 14.2 mg. for normal men but also within the normal range. Also there was no significant difference in the amount excreted by those men who had exophthalmos (9.6 mg.) and by those who did not have exophthalmos (10.6 mg.).

In twelve of the fifteen cases of exophthalmic goiter there was no great change in the excretion of 17-ketosteroids during the administration of iodine; in ten of these, however, there tended to be a slight increase and in two a slight decrease but because of the daily variations in output of 17-ketosteroids that occur in the same subject, these changes cannot be regarded as significant. If a change substantially greater than ± 30 per cent (16) can be regarded as significant then three of the patients (*Cases 4, 5* and *7*) showed a definite increase in their excretion of 17-ketosteroids during iodine treatment. *Case 4* showed very little clinical improvement with iodine; *Case 7* showed slight improvement and *Case 5* showed definite improvement.

In table 2 are given data on seven patients suffering from adenomatous goiter with hyperthyroidism. Like the patients who had exophthalmic goiter, these patients tended to excrete slightly less 17-ketosteroids than the normal average but most of them excreted amounts that fell well within the normal range (notably *Case 18*). Also, there was no constant or significant alteration in the quantity of these

[4] In all instances, except *Cases 1* and *4*, the dose was 10 drops of compound solution of iodine three times per day. In *Cases 1* and *4* the dose was 10 drops five times per day.

[5] The normal subjects used in this study were physicians and technicians working in the laboratories or in the clinic. They did not suffer from any known illness and appeared to be normal in every respect. Their ages ranged from twenty to forty years.

[6] These patients had the exophthalmos that is associated with exophthalmic goiter and the exophthalmos was definite as far as could be judged without actual measurements. No patients who had so-called malignant exophthalmos or who had normal or low metabolic rates were studied.

TABLE 1. DATA ON CASES OF EXOPHTHALMIC GOITER

Case	Age in years and sex	Clinical data	Exophthalmos	Average 17-ketosteroids before iodine, mg. in 24 hrs.	Days after iodine begun	17-ketosteroids, mg. in 24 hrs.	Average 17-ketosteroids during iodine	Per cent change during iodine
1	40 F	Severe toxicity. B.M.R. +66%. Slight improvement with iodine.	Present	4.3 (1)[1]	1 2 7 8 12 13	5.4 5.0 6.4 4.0 5.0 4.7	5.1 (6)[1]	+19
2	25 F	Moderate toxicity. B.M.R. +55%. Definite improvement with iodine; B.M.R. dropped to +29%.	Present	9.0 (1)	1 3 6	10.4 9.2 11.3	10.3 (3)	+14
3	35 F	Moderate toxicity. B.M.R. +63%. Definite improvement with iodine.	Present	8.9 (2)	3 9	11.8 11.3	11.6 (2)	+30
4	38 F	Severe toxicity. B.M.R. +64%. Very little improvement with iodine.	Present	5.6 (2)	3 9 13 16 23	8.3 10.4 7.5 8.9 6.0	8.2 (5)	+46
5	39 M	Moderate toxicity. B.M.R. +66%. Definite improvement with iodine; B.M.R. dropped to +8%.	Present	5.8 (1)	11	11.2	11.2 (1)	+93
6	24 M	Moderate toxicity. B.M.R. +16% and +22%. Definite improvement with iodine.	Present	13.4 (1)	10	14.7	14.7 (1)	+10
7	44 M	Moderate toxicity. B.M.R. +56%. Slight improvement with iodine; B.M.R. fell to +35%.	Present	8.1 (1)	8 19	13.4 10.9	12.2 (2)	+51
8	33 M	Moderate toxicity. B.M.R. +33%. Definite improvement with iodine.	Present	11.3 (2)	4 7	9.2 11.3	10.2	−10
9	67 F	Slight toxicity. B.M.R. +35%. Hypertension. Slight improvement with iodine.	Absent	5.8 (1)	1 5	4.9 7.0	5.9 (2)	+ 2
10	33 F	Moderate toxicity. B.M.R. +39%. Definite improvement with iodine.	Absent	10.1 (2)	1 3	10.8 12.7	11.8 (2)	+17
11	42 F	Moderate toxicity. B.M.R. +48%. Definite improvement with iodine. B.M.R. fell to +38%.	Absent	6.4 (1)	3 7 10	7.5 8.8 8.9	8.4 (3)	+31
12	34 M	Moderate toxicity. B.M.R. +66%. Marked improvement with iodine; B.M.R. fell to +23%.	Absent	10.4 (2)	1 6 8	12.2 13.3 12.6	12.7 (3)	+22
13	52 M	Severe toxicity. B.M.R. +72%. Definite improvement with iodine; B.M.R. fell to +14%.	Absent	11.0 (1)	2 5 9 11	11.5 11.6 10.5 13.2	11.7 (4)	+ 6
14	59 M	Moderate toxicity. B.M.R. +43%. Definite improvement with iodine; B.M.R. fell to +26%.	Absent	9.5 (1)	2 6	7.5 7.6	7.6 (2)	−20
15	29 M	Moderate toxicity. B.M.R. +45%. Definite improvement with iodine; B.M.R. after iodine +35%.	Absent	11.6 (2)	3 5	10.8 14.8	12.8 (2)	+10

[1] Number of assays in parenthesis.

steroids excreted when iodine was administered.

Results obtained for patients who had myxedema or anterior-pituitary insufficiency. The detailed data on ten cases of myxedema and one case of anterior-pituitary insufficiency with a low basal metabolic rate (*Case 33*) are given in table 3. Except in two instances (*Cases 28* and *31*) the level of excretion of 17-ketosteroids was extremely low before treatment with desiccated thyroid. Of the seven women who had myxedema, excluding *Case 28*, the average excretion before thyroid therapy was 1.8 mg. in twenty-four hours. These low levels are comparable to the low levels seen among young children, among women suffering from Addison's disease and in cases of anterior-pituitary insufficiency (see *Case 33*). The patient in *Case 28*, a woman, probably had myxedema but the clinical diagnosis was not definite; this patient excreted 6.7 mg. in twenty-four hours, which is more than the amount excreted by any of the other patients. Only two men suffering from myxedema were studied; in *Case 31* the symptoms of myxedema were of short duration, myxedema having developed two months after thyroidectomy. The excretion of 17-ketosteroids was 6.0 mg., which is however, below the range of excretion for normal men as determined in this study. The other male patient studied (*Case 32*) had spontaneous myxedema and excreted very small amounts before treatment with desiccated thyroid (1.8 mg. and 3.3 mg. of 17-ketosteroids in twenty-four hours). The patient who had anterior-pituitary insufficiency, dwarfism and low basal metabolic rate (*Case 33*) had the lowest excretion of 17-ketosteroids, always excreting less than 1.0 mg. in twenty-four hours even after thyroid medication.

In five cases of spontaneous myxedema (*Cases 23*, *24*, *25*, *26* and *32*) there were extremely slow and slight rises in excretion of 17-ketosteroids after satisfactory treatment with desiccated thyroid. During the period of study after the beginning of thyroid therapy, in none of these cases did excretion reach the normal range. This interval varied from thirteen days to 370 days. Although the patient in *Case 29* had spontaneous myxedema, the effect of thy-

TABLE 2. DATA ON CASES OF ADENOMATOUS GOITER WITH HYPERTHYROIDISM[1]

Case	Age in years and sex	Clinical data	Average 17-ketosteroids before iodine, mg. in 24 hrs.	Days after iodine begun	17-ketosteroids, mg. in 24 hrs.	Average 17-ketosteroids during iodine	Per cent change during iodine
16	61 M	B.M.R. +56%. Improved slightly with iodine.	9.0 (1)[2]	4 6	8.9 9.0	9.0 (2)[2]	0
17	65 M	B.M.R. +50%. Definite improvement with iodine; B.M.R. fell to +38%.	6.4 (1)	1 3	6.8 7.1	7.0 (2)	+ 9
18	41 M	Mild hyperthyroidism. B.M.R. +22%. Slight improvement with iodine.	18.4 (2)	4 6	19.7 18.3	19.0 (2)	+ 3
19	57 F	B.M.R. +26%.	8.8 (2)	1	7.8	7.8 (1)	−11
20	45 F	B.M.R. +54%. Definite improvement with iodine.	4.1 (1)	2 4	4.4 5.6	5.0 (2)	+22
21	41 F	Mild hyperthyroidism. B.M.R. +20%. Slight improvement with iodine.	8.3 (1)	8	6.7	6.7 (1)	−19
22	39 F	B.M.R. +34%. Moderate improvement with iodine.	8.0 (1)	3 7 10	6.0 6.8 8.0	6.9 (3)	−14

[1] Exophthalmos absent.
[2] Number of assays in parenthesis.

roid treatment cannot be evaluated since she was given testosterone propionate during this phase of the study.

The patients who had secondary myxedema of short duration usually showed more prompt and greater rises in 17-ketosteroid excretion with thyroid therapy than did those who had spontaneous myxedema. The patient in *Case 27* had acute thyroiditis three and a half months before the development of myxedema. Although this patient began at low levels of

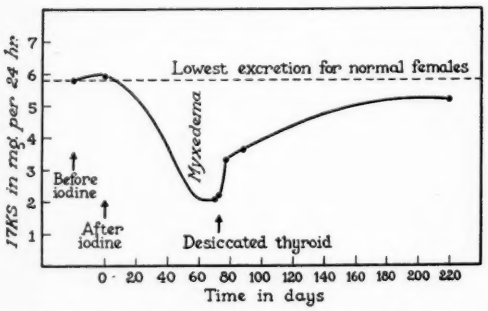

FIG. 1. (*Case 30*). Excretion of 17-ketosteroids in twenty-four hours while the patient was suffering from exophthalmic goiter, while she was receiving iodine pre-operatively, when myxedema had developed post-operatively and while she was receiving desiccated thyroid.

excretion, she reached the normal range for women in about eight days. The patient in *Case 28*, already referred to previously, excreted amounts within the normal range before thyroid treatment was begun and then showed a rapid rise thereafter. The patient in *Case 30* (same as *Case 9* in table 1) is interesting since her 17-ketosteroid excretion had been determined while she was suffering from exophthalmic goiter. At that time she was excreting about 5.8 mg. of 17-ketosteroids in twenty-four hours; two and a half months later, when symptoms and signs of myxedema had developed, the amount had fallen to 2.1 mg. Treatment with thyroid was followed by a slow rise of 17-ketosteroid output to approximately the original level (fig. 1). The patient in *Case 31*, a man, had undergone thyroidectomy two months before the development of myxedema. Within two and a half months after he had begun taking desiccated thyroid he was excreting 17-ketosteroids at the lower range of normal.

The patient who had primary anterior-pituitary insufficiency (*Case 33*) did not show any change in excretion of 17-ketosteroids during treatment with thyroid alone.

COMMENT

The observation that usually there was no change and rarely an increase of the output of 17-ketosteroids while patients who had exophthalmic goiter (Graves' disease) were treated with iodine and that some patients excreted amounts within the normal range, although the average for the group was below normal, indicates that insofar as measurements of urinary 17-ketosteroids reflect testicular and adrenal status there is no fundamental change in function of these glands in cases of exophthalmic goiter. The slight alterations from normal probably can be accounted for by non-specific, secondary effects of the illness similar to those which occur in such miscellaneous conditions as rheumatoid arthritis, ulcerative colitis, surgical operations and anemia (8), in which primary endocrine dysfunction is not suspected. As previously mentioned, Baumann and Metzger (13) and Marine and Rosen (14) reported a decrease of the excretion of biologically active androgens during iodine therapy in cases of exophthalmic goiter. Our studies on the total 17-ketosteroids, which include biologically active androgens and other, inactive, ketosteroids, did not show any consistent change during treatment with iodine. Therefore, if the foregoing observations can be further substantiated there must be an increased excretion of biologically inactive 17-ketosteroids during administration of iodine.

Although Levy Simpson (24) reported beneficial action from testosterone propionate in hyperthyroidism, the experience of Starr and Pomerenze (25) was that it was without effect. Since our observations indicate that the slight and sometimes inconstant changes observed in the excretion of 17-ketosteroids in cases of hyperthyroidism are due to non-specific effects, they do not lend support to the use of testosterone in the general treatment of these patients.

Marine and Rosen (26) observed that exophthalmos experimentally produced in rabbits underwent a recession after gonadectomy. They emphasized their conclusion that func-

tionally active gonads increased the incidence of exophthalmos. Insofar as the excretion of 17-ketosteroids reflects the function of the male gonads or adrenal cortex, our results with human subjects indicate that there is no fundamental quantitative difference or alteration in the function of these glands associated with the presence or absence of exophthalmos and hyperthyroidism.

The observation that untreated patients suffering from myxedema excrete extremely small amounts of 17-ketosteroids indicates that under these circumstances some functions of the adrenal cortex and possibly, in men, the function of the testicles are at a relatively low level. The amounts excreted are close to the amounts found among patients suffering from Addison's disease or from anterior-pituitary insufficiency and among infants. Certainly, changes that occur in the animal organism in cases of hypothyroidism are profound (27–29). Byrom (27) and others have likened the myxedematous state to a reversal toward the mucinous-like state of the fetus and infant. It is not remarkable that the adrenal cortex should be involved in such general changes. Certainly patients suffering from myxedema differ from other subjects in their response to thyroid substance (28–31) and the exact nature of this difference has not been clearly defined.

To attribute the lowered 17-ketosteroid excretion observed in cases of myxedema to a general metabolic disturbance with a resultant depression of the adrenal cortex seems adequate for those patients who have secondary myxedema, that is, myxedema following thyroidectomy or thyroiditis, since there was a significant rise in the excretion of 17-ketosteroids after successful thyroid therapy. This rise was sometimes rapid and sometimes slow but was present in all of our cases. However, such an explanation is inadequate to account for the changes in spontaneous myxedema, since adequate thyroid treatment was without appreciable effect on the excretion of 17-ketosteroids even when followed for as long as one year. An adequate explanation for this result is not apparent. However, a brief consideration of some factors which may be involved is regarded as pertinent.

A more intimate relation between the thyroid and adrenal glands than assumed by the foregoing explanation is implied by the finding that many patients who had Addison's disease due to atrophy of the adrenal glands also exhibited some atrophy of the thyroid gland [Crooke and Russell (32) and Brenner (33)]. It is also pertinent in connection with the excretion of 17-ketosteroids to note that Marine (34) found abnormal atrophy of the interstitial cells of the testis in a case of spontaneous myxedema. It is well to remember, however, that although sexual desire is low or absent it does return with adequate thyroid therapy.

Although the response of most patients who have spontaneous myxedema to thyroid therapy is such that complete failure of the anterior-pituitary gland can hardly be considered, it might be assumed that in some cases spontaneous myxedema of unknown origin differs from secondary myxedema (of known origin) in that it represents a primary partial failure of the pituitary, which adversely affects both the thyroid and the adrenal cortex. If this were the case, the mere treatment of the thyroid failure would not necessarily alter the state of the adrenal cortex nor the excretion of the 17-ketosteroids. The problem of the causation of spontaneous myxedema is of course involved in this hypothesis. Although a comprehensive consideration of this problem is beyond the scope of this paper a few items of evidence will be considered. Goldzieher (35) reported data on a case of simple atrophy of the adrenal cortex associated with hypothyroidism. He also stated that "exceedingly small adrenals were found in two cases of myxedema without any degeneration or interstitial changes of cortex or medulla," and "in the light of present knowledge it must be assumed that lack of pituitary organotrophic stimulation was responsible for both adrenal and thyroid atrophy."

The failure to demonstrate thyrotrophic hormone in the urine of patients suffering from myxedema [Emerson and Cutting (36), Cope (37)] might be considered to favor the hypothesis, since the hormone was found in the urine of thyroidectomized patients. The value of this evidence is uncertain, however, inasmuch as the thyrotrophic activity disappeared from the urine of the thyroidectomized patients in about a year. The results of Thomp-

TABLE 3. DATA ON CASES OF MYXEDEMA AND OF ANTERIOR PITUITARY INSUFFICIENCY

Case	Age in years and sex	Clinical data	17-ketosteroids		Basal metabolic rate	
			Time of determination	Mg. in 24 hrs.	Time of determination	Rate, per cent
23	42 F	Spontaneous myxedema. Cholesterol 427.	Before thyroid	2.1	Before thyroid	−24, −31
			2 days after thyroid	1.4		
			5 days after thyroid	3.1	5 days after thyroid	−25
		Acute depression developed about 6 months after beginning thyroid.	11 days after thyroid	2.3	11 days after thyroid	−22
			14 days after thyroid	3.2	15 days after thyroid	−19
			18 days after thyroid	3.3	20 days after thyroid	−17
			21 days after thyroid	2.9		
			25 days after thyroid	2.4	25 days after thyroid	−15
		Maintenance dose of P.D. thyroid grains 1½.	51 days after thyroid	3.4	51 days after thyroid	−10
			219 days after thyroid	2.3	200 days after thyroid	− 6
24	64 F	Spontaneous myxedema. Cholesterol 378. Pernicious anemia?	Before thyroid	1.5	Before thyroid	−17, −20
			Before thyroid	1.2		
			8 days after thyroid	1.6	6 days after thyroid	−12
			10 days after thyroid	2.1	10 days after thyroid	−11
		Maintenance dose of P.D. thyroid grains 1½.	56 days after thyroid	3.2	56 days after thyroid	− 1
25	47 F	Spontaneous myxedema. Cholesterol 667.	Before thyroid	1.2	Before thyroid	−28, −25
			2 days after thyroid	1.5		
			5 days after thyroid	1.6	6 days after thyroid	−12
		Maintenance dose of P.D. thyroid grains 1½.	9 days after thyroid	1.3	11 days after thyroid	− 8
			13 days after thyroid	2.1	17 days after thyroid	− 2
26	35 F	Spontaneous myxedema. Cholesterol 362. Maintenance dose of P.D. thyroid grains 1.	Before thyroid	1.7	Before thyroid	−24, −28
			46 days after thyroid	1.5	75 days after thyroid	— 2
27	48 F	Myxedema 3½ mo. after acute thyroiditis.	Before thyroid	2.5	Before thyroid	−19, −20
			3 days after thyroid	4.8	3 days after thyroid	−12
			6 days after thyroid	5.5	6 days after thyroid	− 9
			8 days after thyroid	6.3	9 days after thyroid	−12
		Maintenance dose of P.D. thyroid grains 2.	35 days after thyroid	3.8	26 days after thyroid	−13
			166 days after thyroid	8.8	162 days after thyroid	− 9
28	33 F	Thyroidectomy 13 yrs. before. Probable myxedema. Cholesterol 303 and 378. Nervous factors present. Maintenance dose of P.D. thyroid grains 1½.	Before thyroid	6.7	Before thryoid	−23, −31
			Before thyroid	8.6		
			2 days after thyroid	10.2	3 days after thyroid	−14
					6 days after thyroid	−14
			10 days after thyroid	10.2	9 days after thyroid	− 5
29	48 F	Spontaneous myxedema. Cholesterol 396.	Before thyroid	2.1	Before thyroid	−31
			6 days after thyroid	3.6	12 days after thyroid	+ 3
			17 days after thyroid	4.5	28 days after thyroid	+ 2
		Given testosterone propionate, 25 mg. 2 times a week, beginning 19 days after start of thyroid. Maintenance dose of P.D. thyroid grains ¾.	57 days after thyroid	8.6	47 days after thyroid	− 3
			97 days after thyroid	8.1	97 days after thyroid	0
30 (Same pt. as case 9 in table 1)	67 F	Thyroidectomy 2½ mo. before myxedema. Cholesterol 735.	Before thyroid	2.1	Before thyroid	−10
			1 day after thyroid	2.2		
			7 days after thyroid	3.3	9 days after thyroid	− 2
			18 days after thyroid	3.6	15 days after thyroid	− 1
		Maintenance dose of P.D. thyroid grains 1½.	151 days after thyroid	5.1		
31	29 M	Thyroidectomy 2 mo. before myxedema.	Before thyroid	6.0	Before thyroid	−24
			75 days after thyroid	9.7		
			204 days after thyroid	4.6[1]		
		Maintenance dose of P.D. thyroid grain 1.				

[1] We do not have information as to what this patient's B.M.R. was at this time or whether this represents an incomplete collection, since the specimen was sent to us by mail.

TABLE 3. DATA ON CASES OF MYXEDEMA AND OF ANTERIOR PITUITARY INSUFFICIENCY—(*continued*)

Case	Age in years and sex	Clinical data	17-ketosteroids		Basal metabolic rate	
			Time of determination	Mg. in 24 hrs.	Time of determination	Rate, per cent
32	51 M	Spontaneous myxedema. Cholesterol 245.	Before thyroid	1.8	Before thyroid	−30
			Before thyroid	3.3		
			4 days after thyroid	2.9	7 days after thyroid	−26
		Maintenance dose of P.D. thyroid grains 1½.	14 days after thyroid	3.5	12 days after thyroid	−16
			19 days after thyroid	3.9	16 days after thyroid	− 8
					17 days after thyroid	−10
					21 days after thyroid	− 7
			112 days after thyroid	4.5		
			370 days after thyroid	4.0	370 days after thyroid	− 2
33	18 M	Pirmary pituitary insufficiency and low metabolic rate. Dwarfism. Cholesterol 321 and 231. Negative urine prolan. Treated with P.D. thyroid grains ½ to 2.	Before thyroid	0.6, 0.4, 0.8	Before thyroid	−31, −25
			18 days after thyroid	0.6	2 days after thyroid	−34
			22 days after thyroid	0.7	4 days after thyroid	−25
			32 days after thyroid	0.7	5 days after thyroid	−34
			38 days after thyroid	0.9	10 days after thyroid	−42
					11 days after thyroid	−44

son and associates (38) may be considered to be contrary to the hypothesis. They were unable to demonstrate any stimulation of the thyroid glands of fifteen adult patients who had myxedema by administration of preparations of thyrotrophic hormone, although these preparations did stimulate the thyroid glands of other human subjects.

If the primary failure is in the thyroid gland, then changes in the excretion of 17-ketosteroids in cases of myxedema might perhaps be explained by a secondary pituitary dysfunction which affects the adrenal cortex. This thought is suggested by the observation that experimental thyroidectomy is followed by cytologic changes in the anterior-pituitary gland (39). It is not apparent, however, why such an effect on the anterior pituitary should be reversed in secondary myxedema but not in spontaneous myxedema unless the time relations are important. Spontaneous myxedema is an insidious disorder and the patient usually has symptoms long before the nature of the illness is recognized. It is perhaps conceivable that irreparable damage to the pituitary or to the adrenal cortex may occur during the relatively long period during which the disease develops and that this damage may account for the failure of the excretion of 17-ketosteroids to rise during the thyroid therapy. In contrast, in our cases of secondary myxedema the condition was of short duration and the changes in the excretion of 17-ketosteroids appeared to be easily reversible.

It has been assumed in the preceding discussion that the low level of excretion of 17-ketosteroids in cases of myxedema is an indication of impaired adrenal function. It is by no means certain that this assumption is justified, for there is no other evidence that adrenal cortical function is deficient. Rather frequently, patients suffering from anterior-pituitary insufficiency or from Addison's disease have low basal metabolic rates. The administration of thyroid substance to these patients may precipitate a crisis similar to, or identical with, that of adrenal insufficiency (39, 40). Similar reactions have not been reported among patients suffering from myxedema. Stephens (41) subjected a group of patients who had primary hypothyroidism to the salt-deprivation test of Cutler, Power and Wilder (42) and found a normal response to restriction of sodium chloride. No untoward symptoms developed. It was concluded that the patients did not show any evidence of limitation of adrenal cortical function. However, it is well to bear in mind that myxedematous patients have been reported (27) to have relatively large available stores of water and sodium chloride in the extra-cellular, extra-vascular spaces containing the abnormal mucoprotein and that this factor may have influenced the results.

The absence of any evidence of adrenal in-

sufficiency in cases of myxedema [excluding those of so-called pituitary myxedema (43)], although the excretion of 17-ketosteroids remains very low after treatment, suggests further that the amount of 17-ketosteroids in the urine does not reflect the activity of the adrenal cortex with respect to those hormones which are concerned with salt and water balance and with carbohydrate metabolism. It suggests rather that the 17-ketosteroids represent the end products of another activity of the adrenal cortex which is associated with sexual maturity. This interpretation is supported by the fact that children, before the age of puberty, excrete very small amounts of 17-ketosteroids (16); yet there is no question as to the adequacy of their adrenal cortical function.

Certainly the results of the present study are only suggestive. Other investigations concerned with the adrenal cortical function of myxedematous patients are indicated. Undoubtedly, a greater knowledge of the precursors and of the intermediary metabolism of the 17-ketosteroids would aid greatly in clarification of the problems raised.

SUMMARY

In cases of exophthalmic goiter (Graves' disease) the average excretion of 17-ketosteroids was below normal in both sexes and the level of excretion for those patients who had exophthalmos was not significantly different from the level for those patients who did not have exophthalmos. Usually no great changes in the excretion of 17-ketosteroids occurred during iodine therapy, although in a few cases there was an increase. The slight alterations from normal probably can be accounted for by secondary, non-specific effects of the illness.

All the patients who had myxedema, whether secondary or spontaneous, excreted extremely small amounts of 17-ketosteroids during twenty-four hours. During adequate thyroid therapy those cases of secondary myxedema, in all of which the condition was of rather short duration, showed an increase of output of 17-ketosteroids. The cases of spontaneous myxedema did not show this rise during treatment. The possible mechanisms involved in causing this phenomenon are discussed but the precise anatomic or biochemical alteration that the adrenal cortex might exhibit in cases of myxedema is far from clear.

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Effect of Methyl Testosterone Treatment on Muscular Performance and the Central Nervous System of Older Men

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IN AN EARLIER investigation (1) improvement of endurance in dynamic and static work, of finger ergograph performance, of the fusion frequency of flicker and, to a lesser extent, of muscular strength in four male subjects with diminished sexual hormone production (two eunuchoids, two castrates) were reported after four weeks' oral administration of methyl testosterone. An adequate level of male-sex hormone might be important for the maintenance of working capacity. If this is so, then the reduction and final cessation of the sex-hormone production with age might influence the reduction of working capacity with age. In other words, the reduction of working capacity with age might proceed differently if the sex-hormone concentration could be artificially maintained at a higher level. A very large amount of material would be necessary to prove or disprove this hypothesis. In the present paper we are reporting an investigation to determine whether exaggerated fatigue in older men might be partially due to reduction of sex-hormone production. If this is the case, testosterone treatment might be expected to restore partially the working capacity. Complaints of fatigue are very common after forty-five to fifty years, when the loss of working capacity with age becomes more or less noticeable. Each of our six subjects (from 48 to 67 years) complained of excessive fatigability or loss of working capacity, but a thorough and repeated clinical study failed to reveal any pathology, to which increased fatigability could be related. Indeed, the complaints of fatigue were the reason for the prolonged and excellent cooperation of the subjects. The experimental period ranged from six to forty-five weeks in the different subjects.

Methods and experimental procedure were similar to those of our previous study. The following tests were used: (a) endurance in a heavy type of dynamic work, leading to fatigue usually in not more than three minutes; (b) endurance in a type of static work; (c) absolute muscle force in several different muscle groups; (d) recovery of pulse rate after thirty knee bendings and during performance test (a) and (b); (e) maximum tapping rate; (f) fusion frequency of flicker.

The fusion frequency of flicker is that rate of successive light stimuli necessary to produce an effect equal to continuous illumination. The fusion frequency indicates the maximum number of impulses the retino-cortical system is able to receive per unit of time. Thus, the fusion frequency may be looked upon as an expression of the excitability of the retino-cortical system and probably the whole central nervous system. The following fundamental functions are involved in the fusion frequency: chronaxia, latent period and refractory period of the retino-cortical system.

This method has been shown to be an objective and reliable index of the state of the central nervous system in normal fatigue (2), pathological conditions (3), and in drug effects (4, 5).

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METHOD

(*A*) *Dynamic work.* Dumb-bells of eight pounds were lifted one meter with straight arms at a rate of twenty per minute. The work was continued until complete fatigue ensued. The results are given in m-kilos.

(*B*) *Static work.* The subject had to hold the same load as in the dynamic work test with the straight right arm in the horizontal position until complete fatigue supervened.

(*C*) *Recovery of working capacity.* In the types (A) and (B) after complete fatigue, a recovery interval of two minutes was allowed. The subject was then asked to repeat the test. The second performance is lower than the first, because the interval of two minutes is too short for complete restitution, but this difference depends on the recovery speed. At low recovery speed the second performance would be much lower than the first; at high recovery speed the difference between the performances would be small. If the second performance equals the first (=100), the interval of two minutes is sufficient for complete restitution. The recovery speed is expressed by the relative value of the second performance in percentage of the first. This method has been used to study drug effects (6, 7); the variability was found to be less than that of the first performance. Limitations of this method have been discussed recently (8).

The recovery of working capacity after dynamic exercise was investigated in two subjects (*He* and *Kl*) and after static exercise in four subjects (*St*, *He*, *Kl*, *We*). In subject *Ev* no muscular endurance tests could be made because of rheumatism in the arms; however, the muscular strength could be fairly reliably measured, because only single contractions were necessary for this study.

(*D*) *Heart rate.* The heart rate was measured each fifteen seconds for ten seconds during the work and recovery through a stethoscope fixed to the chest at the apex area.

(*E*) *Absolute muscle strength* was measured by means of spring-coil dynamometers in the following muscle group: 1) right hand; 2) left hand; 3) arm extensors; and 4) back muscles. For the measurement of the back-muscle strength, the subject, standing in bowed position with straight knees, seized the handle with both hands and pulled upward. In this test, in addition to the back muscles, other muscle groups are involved, mainly arm and shoulder extensors. Since these were tested separately, the difference between "3" and "4" might be attributed to the back muscles. The error involved in this assumption is probably minor, since the back-muscle strength exceeds that of both arm and shoulder extensors by five times or more.

(*F*) *Maximum tapping rate* was tested by means of a Cenco impulse counter. This method has been described in previous communications (9).

(*G*) *Fusion frequency of flicker.* The same rotator arrangement and procedure was used as in our former investigations (1–5). The accuracy with which the values can be reproduced is high; the variation of the values, taken in the same experiment, does not exceed, as a rule, one to one and one-half cycles. The daily variations do not exceed, as a rule, three cycles, provided the subject's condition is unchanged.

(*H*) *Procedure.* After the initial values were taken, an inert placebo preparation was given for a period from two to six weeks, except in case of one subject (*Ph*). Both preparations were given orally in the same dosage (four tablets a day). Since the taste of the placebos and of methyl testosterone differed, the subjects were told that the effective substance is very small and the same in both tablets, only the compounds were changed. The subjects were vaguely informed that hormone treatment would be tried, but the actual preparation was unknown to them.

Methyl testosterone[2] tablets were given four times a day (40 mg.) for the first three to six weeks; later the dosage was changed as indicated in table 1. The experiments were performed at intervals from three to six weeks, in order to exclude any possible influence of training. Some training effects have been observed (10) when exercise tests were repeated at weekly intervals, but no training effects have been described for longer time intervals.

RESULTS

Table 1 gives a summary of the results.

Fusion Frequency of Flicker. The fusion frequency of flicker (fusion frequency) was not influenced by placebo administration in any of these subjects. The failure to influence the fusion frequency by placebos was observed in an earlier study (10). Methyl testosterone treatment produced a significant increase in all subjects and in two subjects a very pronounced increase. The increase was least pronounced in our oldest subject *We* (67 years); this is not surprising since the fusion frequency declines with age (11). Subjects *Ev*, *St*, *He* and *Kl* had subnormal pre-treatment values (below forty flashes per second). Methyl testosterone treatment increased the fusion frequency to such extent that the values fell within normal range. The increase of the fusion frequency could be observed after three to six weeks in subjects *Ev*, *St*, *He* and *Ph*, after three months in subject *We*, and after six months in subject *Kl*; however, the latter subject was treated for several weeks with an insufficient dosage of 20 mg. a day and then with the barely sufficient dosage of 30 mg. a day.

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[2] Our thanks are due to Dr. Max Gilbert of the Research Department of the Schering Corporation for the supply of Oreton-M tablets containing methyl testosterone.

Dynamic Work. No significant placebo effects were observed in subjects *Kl* and *We*. Methyl testosterone treatment produced a marked increased of the work performance by testosterone treatment, does not appear to be significant. The uncontrolled increase of 100 per cent in subject *Ph* is probably significant. No determinations were made in subject *Ev*.

TABLE 1. EFFECT OF METHYL TESTOSTERONE TREATMENT (M.T.) ON FUSION FREQUENCY OF FLICKER, ON ENDURANCE, AND MUSCLE STRENGTH

Subj. Age	Daily Dosage	Treatment Period 1942–1943 from	to[1]	Fus. Fr. Flashes per sec.	Dynamic Work m-kilos	Endur. Stat. Work seconds I	II	I &II	Muscle Handgrip (kilos) Rt.	Lt.	Strength Arm Extens.	Back Muscles
Ev	none	—	12/ 5	35.6	—	—	—	—	42	45	38	225
58	placebo	12/ 6	1/ 2	35.2	—	—	—	—	50	45	35	300
	40 mg. M.T.	1/ 3	1/23	38.4	—	—	—	—	50	42	35	275
	40 mg. M.T.	1/23	2/13	40.8	—	—	—	—	52	46	40	350
St	none	—	12/ 5	36.8	506	48	36	84	44	37	36	300
58	placebo	12/ 6	1/ 2	36.0	608	45	42	87	45	39	34	300
	40 mg. M.T.	1/ 3	1/23	40.2	>1300	55	45	100	46	36	35	375
	40 mg. M.T.	1/23	2/ 6	40.8	>1300	60	51	111	45	39	35	375
	20 mg. M.T.	2/ 7	2/27	44.4	>1300	56	55	111	49	40	35	375
	20 mg. M.T.	2/27	3/27	48.0	>1300	54	53	107	53	44	35	450
He	none	—	11/20	39.2	330	62	50	112	45	53	42	225
48	none	11/20	11/28	38.0	362	55	40	95	45	51	35	250
	placebo	11/29	1/16	38.4	578	45	38	83	40	48	35	250
	40 mg. M.T.	1/17	2/13	42.4	594	52	45	97	40	50	36	350
	40 mg. M.T.	2/13	3/13	45.6	608	65	50	115	35	44	37	325
	40 mg. M.T.	3/13	4/10	47.6	636	60	50	110	41	49	37	325
	40 mg. M.T.	4/10	5/15	47.2	—	56	42	98	45	49	42	350
Kl	none	—	12/12	39.2	202	30	30	60	42	35	42	200
57	placebo	12/13	1/ 9	38.4	216	30	29	59	43	35	42	200
	40 mg. M.T.	1/10	1/30	39.6	238	36	32	68	43	37	35	250
	40 mg. M.T.	1/30	2/20	39.2	348	42	40	82	43	36	39	275
	20 mg. M.T.	2/21	3/27	36.0	238	37	35	72	41	32	40	250
	30 mg. M.T.	3/28	4/24	38.8	260	37	32	69	45	38	41	350
	30 mg. M.T.	4/24	6/19	39.2	—	35	30	65	45	37	41	325
	30 mg. M.T.	6/19	7/17	45.0	304	45	42	87	45	35	41	325
	none	7/18	8/21	42.4	—	35	30	66	42	35	40	275
	none	8/21	9/16	39.2	248	38	36	74	45	35	42	212
	30 mg. M.T.	9/17	10/30	39.6	—	44	42	86	44	34	39	250
	30 mg. M.T.	10/30	11/27	40.0	—	44	40	84	50	40	35	270
Ph	none	—	6/ 1	46.4	248	35	—	—	60	52	41	300
51	40 mg. M.T.	6/ 2	6/23	47.8	—	70	—	—	60	52	41	350
	40 mg. M.T.	6/23	7/22	52.0	596	90	—	—	64	54	44	380
We	none	—	4/24	42.4	258	30	28	58	42	47	34	175
67	placebo	4/25	5/ 3	40.8	276	50	45	99	44	47	32	167
	40 mg. M.T.	5/ 4	6/ 2	42.0	362	48	45	93	42	47	32	200
	40 mg. M.T.	6/ 2	6/28	42.4	—	55	—	—	45	44	34	—
	40 mg. M.T.	6/28	7/29	45.0	492	65	55	120	45	47	35	225

[1] This column shows the dates of measurement.

61 and 79 per cent (table 2). In subject *St*, placebo administration increased the work performance by 20 per cent; compared to this increase, the methyl testosterone effect is enormous; in fact, the subject would have been able to continue the work beyond the time at which the exercise was discontinued by the experimenter. In subject *He*, placebo administration produced so large an increase of performance that the further increment, after methyl It appears that methyl testosterone treatment increased significantly the work performance in four of five subjects, while the increase was only slight in the fifth subject, *He*.

Static Work. The third group of columns of table 1 shows the results on endurance in static work, first performance, second performance, and the sum of both. No placebo effects were observed in subjects *St*, *He*, and *Kl*. Methyl testosterone treatment produced significant

increases in subjects *St* and *Kl*, and no effect in subject *He*. Subject *We* responded to placebo administration with a marked increase and with a further, rather large increase to methyl testosterone. In this subject, a psychological factor in regard to the static work can not be entirely ruled out. Subject *Ph* responded with a very large increase of endurance; the significance of this is brought into question by the absence of placebo control. The effect was more manifest in the second work performance in subject *St* and about equal in first and second performance in subjects *Kl* and *We*.

Muscle Strength. The most pronounced effects of methyl testosterone treatment were obtained on the back muscles. No, or insignificant, placebo effects were observed in subjects *St*, *He*, *Kl*, and *We* who showed a marked increase after methyl testosterone treatment. Subject *Ev* showed a marked increase after placebo administration, a slight drop during the first three weeks of methyl testosterone treatment, and a marked increase during the following three weeks' treatment. Subject *Ph* (not controlled by placebos) responded with a gradual and marked increase. A slight increase of handgrip strength was observed in subject *Kl* and *Ph* and a somewhat larger increase in subject *St*. The increase occurred later than the effect on the back muscles and was of much smaller magnitude. No effect was seen in subject *He* and *We* and only a slight effect, of questionable significance, in subject *Ev*. No effect on the strength of arm extensors was observed in any of the subjects.

No consistent effects were observed on the increase and recovery of the heart rate during and after dynamic and static work and after thirty knee-bendings, performed within one minute, and on the maximum tapping rate.

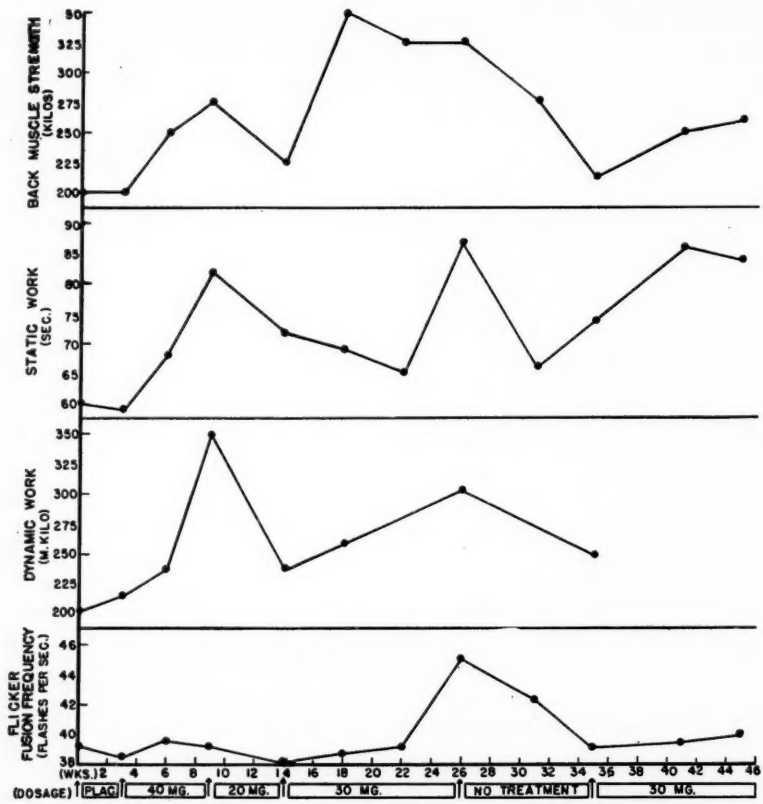
Table 2 shows the maximum effects of methyl testosterone treatment compared to pre-treatment values. Pre-treatment values are taken as those which were highest either before or after the placebo period. The effect on the fusion frequency is expressed as absolute difference in flashes per second, the effect on the muscular performance tests as percentage increase. In subject *St*, *Kl* and *We* the effect on the dynamic-exercise performance was greater than the effect on static exercise, while in subject *Ph* static exercise showed the greater increase. The maximum increase of handgrip strength (right) varied between 0 and 17.5 per cent (average 5.9 per cent), compared to an increase from 27 to 75 per cent (average 46.1 per cent) of the back-muscle strength.

Table 1 shows that it is possible to maintain the effect on the fusion frequency of flicker and on back-muscle strength for a prolonged period (six weeks in subject *Ev*, twelve weeks in subject *St*, four months in subject *He*, eight months in subject *Kl*, seven weeks in subject *Ph*, and about three months in subject *We*). In subject *St*, 20 mg. methyl testosterone daily was sufficient to maintain or even to increase the effect previously obtained with 40 mg. of that substance. On the other hand, 20 mg. methyl testosterone was not sufficient to maintain the back-muscle strength in subject *Kl*, while a daily dosage of 30 mg. again produced an increase. The same dosage increased the fusion frequency of flicker after several months. It is interesting to note how long accumulation might be necessary to produce effects with

TABLE 2. MAXIMUM EFFECT OF METHYL TESTOSTERONE TREATMENT (B) COMPARED TO HIGHEST PRE-TREATMENT LEVEL (A)

Subject	*Ev*	*St*	*He*	*Kl*	*Ph*	*We*
Flicker Fusion Freq. Flashes/sec.						
A	35.6	36.8	39.2	39.2	46.4	42.4
B	40.8	48.0	47.6	45.0	52.0	45.0
Incr. flashes	5.2	11.2	8.4	5.8	5.6	2.4
Dynamic Work m—kilos						
A	—	608	578	216	248	274
B	—	>1300	636	348	596	492
Per cent incr.	—	> 114	10	61	100	79
Static Work						
A	—	84	112	60	35	99
B	—	111	115	87	90	120
Per cent incr.	—	31	2.5	45	157	21
Handgrip Right						
A	50	45	45	43	60	44
B	52	53	45	45	64	45
Per cent incr.	3.8	17.5	0	4.5	6.5	2.1
Arm Extensors						
A	38	36	42	42	41	34
B	40	35	42	42	44	35
Per cent incr.	5.0	− 2.5	0	0	7.1	2.9
Back Muscles						
A	225	300	250	200	300	175
B	350	450	350	350	380	225
Per cent incr.	56	50	40	75	27	28.5

barely sufficient dosage.[3] The accompanying figure shows that the effect must be attributed to methyl testosterone treatment rather than to interference of other factors as they might occur in prolonged experiments. The fusion frequency dropped to the pre-treatment value again. The figure shows also the parallelism between dosage and the muscular-performance tests, in that the performance tends to increase in the periods with 40 and 30 mg. and to decrease with the 20-mg. dosage or after cessation of administration.


BACK MUSCLE STRENGTH (KILOS)
STATIC WORK (SEC.)
DYNAMIC WORK (M. KILO)
FLICKER FUSION FREQUENCY (FLASHES PER SEC.)
(WKS.) 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
(DOSAGE) PLAC 40 MG. 20 MG. 30 MG. NO TREATMENT 30 MG.

Effect of methyl testosterone dosage upon (a) back-muscle strength, (b) endurance in static-work performance (c) dynamic-work performance, and (d) fusion frequency of flicker. The beginning and variation of treatment are indicated by arrows beneath the abscissa (weeks). Placebo administration does not show significant effects. In all muscle-performance tests (a, b, c) there is a peak at the end of the 40 mg. period (ninth week); a drop during the following 20 mg. period; a renewed increase during the 30 mg. period, with the peak of back-muscle strength in the eighteenth week and of static and dynamic performance in the twenty-sixth week; a drop after cessation of treatment; and increase again after renewal of treatment with 30 mg. (back-muscle strength and static performance only). The fusion frequency (d) shows no significant reaction before twenty-two weeks; a peak is reached at the end of the 30-mg. period (twenty-sixth week), from which it drops after cessation of treatment and slowly increases again after renewal of 30-mg. administration.

when the treatment was interrupted and it increased slowly after the treatment was started

[3] Older patients with prolonged testosterone treatment should be periodically examined with rectal palpation in order to detect any possible untoward development in the prostate gland.

DISCUSSION

Comparison of a placebo and an experimental period does not exclude psychological factors which might influence the results during the experimental period; the placebo period

rather reveals subjects susceptible to suggestive effects. It is improbable, however, that suggestive effects could be maintained over so long a period. Furthermore, the pattern of placebo effects appears to be more irregular than the methyl testosterone effects. Methyl testosterone treatment produced a significant increase of back-muscle strength in all subjects, placebo administration in only one subject, *Ev.* Performance of dynamic work was significantly increased by placebos in subject *St, He,* and slightly in subject *Kl* without increase of static-work performance, while the opposite response was observed in subject *We.* All subjects, except *He,* responded to methyl testosterone treatment with increase of both static-work and dynamic-work performance. Subject *He* was also consistent in so far as he showed no increase either of dynamic or of static performance. It is interesting that in the same subject different work-performance tests respond differently to suggestion (placebo administration). The more uniform and prolonged action of methyl testosterone treatment and its greater magnitude suggest that the androgen effects on the work-performance tests are real. Confirmatory to this conclusion is the consistently different action upon different muscle groups and the failure to increase the maximum tapping rate. Furthermore, the methyl testosterone effect on the fusion frequency of flicker is objective.

The increase of the fusion frequency of flicker in all subjects suggests that the fatigability of central nervous-system functions in this age group is influenced by the reduction of sex-hormone production. These results corroborate those obtained by methyl testosterone treatment in eunuchoids and castrates (1). In this connection it is interesting to recall Pavlov's experiments (12) on the destruction of the normal pattern of conditioned reflexes after castration and Katai's (13) observations of measurable atrophic changes in the brain and spinal cord of white rats deprived of their testes.

The magnitude of methyl testosterone effects on dynamic and static exercise in older men is about the same as that observed in younger subjects with abnormally reduced sex-hormone production (1), while the increase of back-muscle strength is much greater. On the other hand, no effect on the pulse rate was seen in this series, while younger eunuchoids and castrates showed a lesser increase during exercise and faster recovery.

Of special interest is the action of methyl testosterone treatment upon the back muscles. According to Rejs (14), who studied the decline of muscle strength of different muscle groups with age in three thousand men and women, the drop of back-muscles strength with age is more pronounced than that of other muscles. Changes of posture, which depends largely on back-muscle tonus, are in fact a common feature of aging. This parallelism seems to indicate that methyl testosterone treatment counteracts some effects of aging. The failure of the androgen treatment to increase the performance of normal young men (15), in whom the sexual hormone production is at its maximum, seems to corroborate these conclusions.

Since this experimental group consisted of subjects who complained of exaggerated fatigue, the results can not be applied to older men who do not complain of increasing fatigability. Similarly, it can not be expected that all or even a majority of older men complaining of fatigue will respond to methyl testosterone. Increased fatigability might be due to quite different processes (16) and this experimental group is much too small to provide conclusions regarding frequency distribution. The positive effect of methyl testosterone treatment, however, appears to be safely established in this experimental group and is encouraging for further investigations.

SUMMARY

In six male subjects between 48 and 67 years of age, complaining of fatigability but without any clinical symptoms, oral treatment with 30 to 40 mg. methyl testosterone increased significantly, compared to a placebo period, the fusion frequency of flicker and back-muscle strength. The performance was increased in dynamic and static work in four of five subjects. No effect was noted on the strength of arm extensors and only a slight increase of questionable significance in handgrip strength in two of six subjects. The positive effect on the fusion frequency, back-muscle strength or dy-

namic-work and static-work performance was maintained up to eight months. A dosage of 20 mg. was sufficient to maintain the effect previously attained with 40 mg. in one subject and was insufficient in another. No effect was observed in maximum tapping rate and heart rate in exercise and recovery. The results appear to be compatible with the hypothesis that maintenance of a higher level of male sex hormone has an influence on the depression of working capacity with age.

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Tiselius Electrophoresis Studies of Plasma Proteins in Diabetes Mellitus

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Plasma proteins in diabetes mellitus have been extensively studied in the past; chemical precipitation has been used for estimating the albumin-globulin content. In hopes that further information might be obtained on changes in plasma-protein fractions in various stages of the disease, electrophoresis studies were undertaken.

MATERIALS AND METHODS

Longworth's modification of the Tiselius electrophoretic method was used to estimate the albumin, α-globulin, β-globulin and γ-globulin as well as fibrinogen in the plasma. Phosphate buffer solution of pH 7.8, ionic strength 1.6, was employed. Normal values determined in this laboratory on 21 normal subjects have been described(1). Total protein values were determined by Pregl's modification of the micro-Kjeldahl method for estimating total and nonprotein nitrogen.

The plasma, diluted with buffer after dialysis against the buffer solution for three days, is placed in a Tiselius cell (U shaped tube) and a boundary is formed by moving the buffer solution over the plasma. An electric current is then passed through the buffer, buffer-protein solution. The various plasma proteins move at different rates, the albumin having the highest speed and the γ globulin the slowest. By passing light through the solution after the separation of the various proteins, a definite band can be seen for each protein. The relative amounts of the various proteins may be estimated by using the scanning adaptation of the Tåepler-Schieren method as described by Longsworth (2) which gives a complete picture. The area under a peak in a picture, or pattern caused by a boundary, is proportional to the total concentration of that particular boundary. The method and physical principles on which it is based have been well reviewed by Moore (3).

Thirty patients with diabetes were studied. Two groups were represented. The first was characterized by uncomplicated and uncontrolled diabetes with or without acidosis. The second group comprised cases of controlled diabetes complicated by diabetic retinitis, usually with increased capillary fragility but without any other apparent complication. One patient with moderately severe diabetes complicated by extensive cellulitis (*Staphylococcus aureus*) of the face was studied.

By the term "control" of the diabetes mellitus as used in this paper we imply maintenance of normal blood sugar both before and four hours after eating and of sugar-free urine before each meal and at bed time, so far as this is possible. Patients in whom this degree of control was not possible to attain were omitted from the "uncomplicated" group. In the group with retinitis this degree of control could not be attained in the cases indicated.

Capillary fragility was determined by a modification of the Rumpel-Leeds method. The blood-pressure cuff was applied to the lower portion of the upper arm, inflated to the diastolic level, and allowed to remain in place three minutes. The petechiae appearing in the ante-cubital area in a circle one inch in diameter were counted. Capillary fragility was considered to be increased if more than 20 petechiae were present. Often they were too numerous to count.

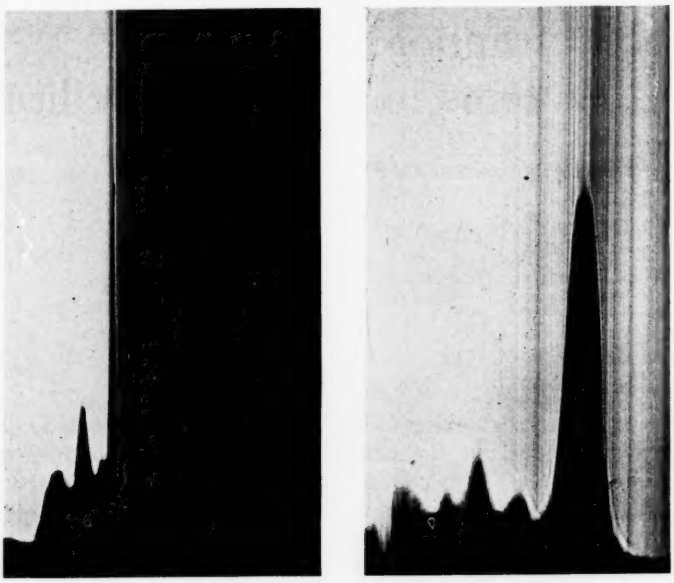

CHART 1. Tiselius plasma-protein pictures of patient 1. *A*, untreated diabetes with acidosis. *B*, well controlled diabetes with no complications.

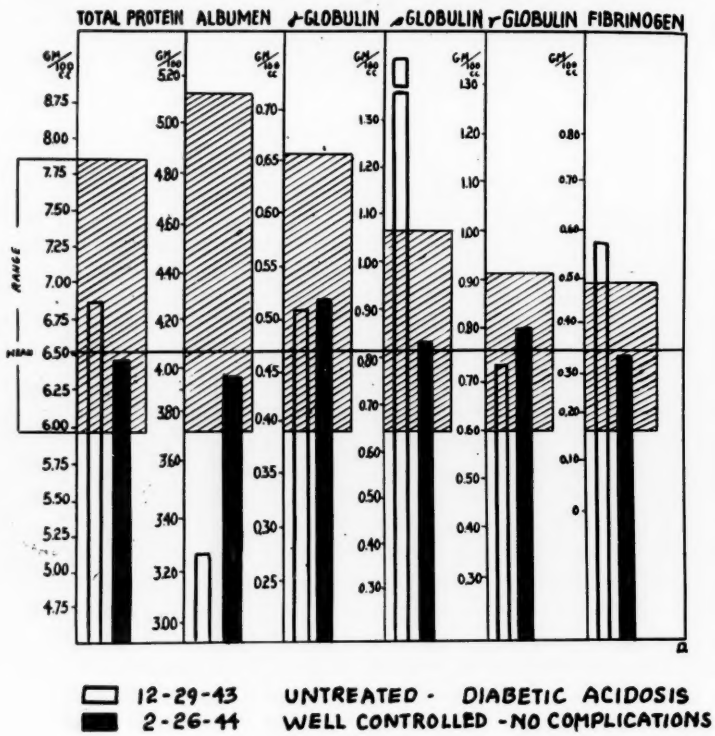

CHART 2. Plasma proteins of patient 1.

TABLE 1. PLASMA PROTEIN FRACTIONS IN DIABETES MELLITUS WITHOUT ACIDOSIS

Diagnosis and Case No.	Total Protein Gm./100 ml.	Albumin Gm./100 ml.	Albumin % Total Protein	α Globulin Gm./100 ml.	α Globulin % Total Protein	β Globulin Gm./100 ml.	β Globulin % Total Protein	γ Globulin Gm./100 ml.	γ Globulin % Total Protein	Fibrinogen Gm./100 ml.	Fibrinogen % Total Protein
Normal (21 controls)											
Average	6.51	4.09	62.7	0.47	7.2	0.81	13.1	0.77	11.7	0.33	5.4
Range	5.94–7.82	3.72–5.11	60.1–67.2	0.39–0.66	6.0–8.7	0.65–1.07	11.0–15.9	0.60–0.91	8.6–14.8	0.16–0.48	2.8–7.2
Uncontrolled Diabetes											
4	6.90	3.80	55.2	0.45	6.5	0.66	9.6	1.15	16.6	0.84	12.1
5	5.52	3.40	63.0	0.38	6.8	0.85	15.4	0.54	9.8	0.26	4.8
6	5.97	3.77	63.0	0.42	7.0	0.98	16.6	0.55	9.1	0.26	4.3
7	6.38	3.67	57.5	0.56	8.8	0.81	12.6	0.87	13.7	0.47	7.4
8	6.02	3.62	60.0	0.55	9.1	0.86	14.4	0.64	10.6	0.35	4.8
Average	6.16	3.65	59.8	0.47	7.6	0.83	13.7	0.95	12.0	0.43	7.3
Range	5.52–6.90	3.40–3.80	55.2–63.0	0.38–0.56	6.5–9.1	0.66–0.98	9.6–16.6	0.54–1.15	9.1–16.6	0.26–0.84	4.3–12.1
Well Controlled Diabetes											
5	5.90	3.78	64.2	0.32	5.3	0.91	15.5	0.60	10.1	0.29	4.9
9	5.97	3.64	61.1	0.47	7.8	0.77	12.9	0.82	13.7	0.27	4.5
10	7.56	4.39	58.2	0.67	8.9	1.28	17.0	0.69	11.2	0.35	4.6
11	6.83	3.96	58.4	0.54	7.9	1.02	14.8	0.82	11.8	0.49	7.1
12	6.22	3.83	60.5	0.45	7.1	0.66	10.5	0.84	13.3	0.54	8.6
13	6.01	3.57	59.4	0.34	5.7	0.84	13.9	0.77	12.8	0.47	7.9
14	6.86	4.17	60.8	0.66	9.6	1.33	19.4	0.47	6.8	0.23	3.4
Average	6.48	3.90	60.4	0.49	7.4	0.97	14.8	0.71	11.4	0.38	5.8
Range	5.90–7.56	3.57–4.39	58.1–64.2	0.32–0.66	5.3–9.6	0.66–1.33	10.5–19.4	0.47–0.84	6.8–13.7	0.23–0.54	3.4–8.6

RESULTS

The studies made on two patients with uncontrolled diabetes and severe acidosis showed a normal total protein but a reduced albumin and an increased β-globulin. Chart 1 shows the Tiselius protein pictures in one of these cases. Studies were obtained both before any therapy and after careful diabetic management for months. As shown in chart 2, which presents the data obtained from the pictures in chart 1, the protein picture returned to normal after several months of diabetic control and adequate nutrition. The second case showed similar changes.

Eleven patients with varying degrees of diabetes mellitus but without acidosis were studied. Five determinations obtained before diabetic management showed a total protein in the lower range of normal or slightly below and an essentially normal protein distribution. Seven studies taken after careful diabetic management revealed the total protein and fractional distribution of the protein to be normal (table 1) except for a slightly lowered plasma albumin in *Cases 9* and *13*. *Case 9* had mild peripheral neuritis, and *Case 13* soon afterward was found to have carcinoma of the tongue. It is interesting that in *Case 2* the total plasma protein, which was low before treatment, became normal after several months of control. The elevated β-globulin observed in *Cases 10* and *14* is unexplained.

The Tiselius plasma-protein picture shown in chart 3 was obtained in the case of diabetes (*No. 3*) complicated by severe *Staphylococcus aureus* infection. In this case the total plasma protein was 6.50 gm. per 100 ml. There was a marked increase in α-globulin and β-globulin. The α-globulin was 1.32 gm. and the β-globulin 1.35 gm. per 100 ml. The increase in α-globulin in this case was probably due to the infection. A high α-globulin is frequently observed in infections.

Sixteen patients with diabetic retinitis were studied after weeks or months of careful diabetic control (tables 2 and 3). All showed a nor-

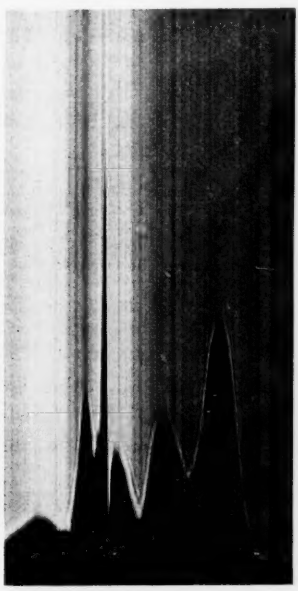

CHART 3. Tiselius plasma-protein picture of diabetic patient (No. *3*) with *Staphylococcus aureus* infection.

TABLE 2. PLASMA PROTEIN FRACTIONS IN WELL CONTROLLED DIABETES WITH DIABETIC RETINITIS WITHOUT AND WITH A HIGH PROTEIN DIET

Case No.	Protein Gm./Day of Diet	Days on Diet	Complications	Total Protein Gm./100 ml.	Albumin Gm./100 ml.	Albumin % Total Protein	α Globulin Gm./100 ml.	α Globulin % Total Protein	β Globulin Gm./100 ml.	β Globulin % Total Protein	γ Globulin Gm./100 ml.	γ Globulin % Total Protein	Fibrinogen Gm./100 ml.	Fibrinogen % Total Protein
15	62	60	Minute hemorrhages macula area	6.00	3.46	57.6	0.43	7.2	1.15	19.2	0.62	10.3	0.34	5.7
	80	40	Eyes definitely better	6.42	3.70	57.6	0.55	8.6	1.07	16.7	0.70	10.9	0.40	6.2
16	62	30	Diabetic retinitis, hypertension, capillary fragility	6.23	3.58	57.6	0.48	7.7	0.94	15.0	0.79	12.7	0.44	7.0
	86	90	Eyes definitely better	6.39	3.83	59.9	0.41	6.6	0.90	14.1	0.79	12.2	0.46	7.2
17[1]	56	235	Retinitis, capillary fragility	6.12	3.37	55.0	0.36	5.8	1.37	22.6	1.02	16.6		
	80	30	"Eyes better than last visit; no new hemorrhages"	6.42	4.03	62.5	0.53	8.3	0.76	12.0	0.61	9.5	0.49	7.7
18	80	120	Diabetic retinitis diabetic neuritis, angina pectoris	6.15	3.15	51.6	0.75	12.3	0.99	16.2	0.80	13.1	0.44	6.8
	80 plus 2 tbs. protein digest t.i.d.	95		6.69	3.53	52.8	0.75	11.2	1.20	18.0	0.76	11.3	0.45	6.7
	120	30	"Says she can see better"	6.38	3.62	56.5	0.67	10.5	1.05	16.6	0.70	11.0	0.34	5.4
	120	93		6.47	3.96	61.1	0.68	10.5	1.10	17.1	0.50	7.7	0.23	3.6
19	62	240	Hemorrhagic neuroretinitis	6.04	3.36	55.5	0.30	4.9	1.06	17.7	0.96	15.9	0.36	6.0
	100	49	Eyes not improved	6.44	3.77	58.4	0.46	7.2	1.02	15.8	0.73	11.4	0.46	7.2
20	59	90	Diabetic retinitis, capillary fragility	6.54	3.43	52.5	0.38	5.8	1.26	19.2	1.12	17.1	0.35	5.4
	100	94	No new hemorrhages	7.10	3.99	56.2	0.28	3.9	0.92	13.0	1.24	17.5	0.67	9.4
21	95	120	Hemorrhagic retinitis, cataracts, essential hypertension	5.56	3.08	56.0	0.49	9.0	1.08	19.7	0.49	8.8	0.36	6.5
	95	240	Eyes showed no change	5.72	2.97	51.9	0.50	8.8	1.07	18.7	0.65	11.4	0.53	9.2

[1] Diabetes difficult to control.

mal or slightly decreased total protein but a low plasma albumin. In the majority of cases the albumin fraction was decidedly lower than in uncontrolled, uncomplicated diabetes mellitus. The β-globulin was significantly elevated.

Seven of these patients were studied on several occasions, and the effect of a high protein diet was observed in six of them. After a period of three to six months of this regimen the total plasma protein increased. In five of the six cases the increase was accompanied by an increase in the percentage of albumin. In the sixth case the percentage remained unchanged, but the absolute albumin level rose from 3.46 to 3.70 gm. per 100 ml. During the period of time covered by these studies, which was relatively short, the retinitis appeared to improve in four of the six cases.

Case 21 was studied on several occasions while receiving a 2100 calorie diet containing

TABLE 3. PLASMA PROTEIN FRACTIONS IN WELL CONTROLLED DIABETES WITH DIABETIC RETINITIS

Case No.	Protein Gm./Day of Diet	Days on Diet	Complications	Total Protein Gm./100 ml.	Albumin Gm./100 ml.	Albumin % Total Protein	α Globulin Gm./100 ml.	α Globulin % Total Protein	β Globulin Gm./100 ml.	β Globulin % Total Protein	γ Globulin Gm./100 ml.	γ Globulin % Total Protein	Fibrinogen Gm./100 ml.	Fibrinogen % Total Protein
22[1]	57	20	Proliferating retinitis, capillary fragility	6.59	3.72	56.4	0.49	7.4	1.18	18.0	0.83	12.6	0.37	5.6
23	50	49	Diabetic retinitis, arteriosclerosis, capillary fragility	6.10	3.11	51.0	0.58	9.5	1.24	20.3	0.88	14.4	0.29	4.8
24	50	160	Diabetic retinitis, capillary fragility	6.49	3.68	56.8	0.42	6.5	1.11	17.0	0.88	13.5	0.40	6.2
25	71	?[2]	Cataracts, possible hemorrhagic retinitis, proliferating retinitis	6.62	3.26	49.2	0.56	8.4	1.39	21.0	0.91	13.8	0.50	7.6
26	65	551	Diabetic retinitis, capillary fragility	6.42	3.30	51.4	0.61	9.5	0.95	14.7	0.91	14.2	0.65	10.2
27	68	305	Diabetic retinitis, capillary fragility	6.07	3.08	50.8	0.38	6.2	1.10	18.1	1.13	18.7	0.38	6.2
28	90	365+	Diabetic retinitis, capillary fragility	6.24	2.95	47.4	0.37	5.9	1.44	23.1	0.87	13.9	0.61	9.7
29	77	929	Diabetic retinitis, capillary fragility	5.97	3.36	55.3	0.42	7.1	1.00	16.8	0.84	14.0	0.35	5.8
30	62	467	Diabetic retinitis, capillary fragility	6.04	3.40	57.2	0.33	5.5	1.06	17.9	0.84	14.1	0.31	5.3
	Average			6.28	3.32	52.8	0.47	7.3	1.16	18.4	0.89	14.4	0.43	6.8
	Range			5.97 to 6.62	2.95 to 3.72	47.4 to 56.8	0.33 to 0.61	5.5 to 9.5	0.95 to 1.44	14.7 to 23.1	0.83 to 1.13	12.6 to 18.7	0.29 to 0.65	4.8 to 10.2

[1] Diabetes difficult to control.
[2] Referred case; definite time unknown.

95 gm. of protein. No significant modification in the total protein or fractions was observed. The low total protein may likely be explained by a constant moderate albuminuria.

Case 29 is particularly interesting because excellent diabetic control had been maintained for almost four years at the time the plasma-protein study was made; 100 mg. cevitamic acid per day had been taken during this period. Despite this treatment increased capillary fragility persisted, and a low plasma albumin was found.

DISCUSSION

The marked increase in the plasma β-globulin fraction in the cases with diabetic acidosis may have been partly due to the high lipid and cholesterol content. Longsworth, Shedlovsky, and MacInnes obtained results that suggested a "combination between lipids and β-globulin" (4).

A high α/A ratio was reported in febrile patients by Longsworth and co-workers (4) and in pneumonia patients by Blix (5). The results on the diabetic patient with a *Staphylococcus aureus* infection show similar changes in the α-globulin.

Patients with uncontrolled uncomplicated diabetes who had a low albumin on initial study developed a normal total protein and albumin on diabetic management and a diet containing a maintenance amount of protein. However, the picture did not return to normal in patients with diabetic retinitis but did so only after the protein intake was increased by 20 to 60 gm. per day. Recovery was very slow in both cases. This suggests that tissue-protein deficiency was probably associated with the low plasma-albumin level.

The relatively long period required for restoration of the plasma-albumin level in the diabetic patient is in contrast with that required in dogs with hypoalbuminemia produced by protein-deficient diets (6). The serum-albumin depletion induced by a three weeks' fast was completely corrected within one week by a diet consisting solely of meat *ad lib.* Approximately 50 gm. per kilogram per day was ingested. Of course, it was impossible for the patients to attain such a high protein intake.

Since the retinitis in cases treated with high protein diets apparently tended to improve, these studies suggest that a much higher protein diet than is customarily employed in treatment of diabetes may prove helpful in the management of diabetic retinitis.

From the results obtained on the patients with diabetic retinitis it appears that a low plasma albumin is associated with this change. No evidence is presented as to which occurs first.

Further studies are now being carried on to correlate these findings with those obtained on rabbits with alloxan diabetes with and without retinal hemorrhages.

SUMMARY

Tiselius electrophoresis studies of plasma proteins were carried out on 30 patients with diabetes mellitus.

In severe uncomplicated diabetic acidosis the total protein value was normal but albumin was low and β-globulin very high. After treatment and maintenance of good nutrition for months the picture became entirely normal.

In mild untreated diabetes the protein distribution was normal but the total protein was slightly decreased. After adequate therapy on a standard diet containing not more than 80 gm. of protein, the plasma protein became normal.

In diabetes complicated by diabetic retinitis the plasma albumin was low despite apparently excellent diabetic control. When patients were placed on a very high protein diet the picture was restored to nearly normal levels and the eye condition was apparently improved in some instances.

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Limitations and Complications of Organotherapy in Male Homosexuality

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IN VIEW of the conflicting reports of the efficacy of organotherapy in the clinical management of the male homosexual it is desirable to report further therapeutic experience so that the added weight of numbers of cases treated will eventually facilitate an evaluation of hormone therapy of homosexuality. In the course of an extended study of the biological and temperamental characteristics of homoerotic and homosexual individuals it was deemed advisable to make a series of clinical trials of organotherapy in a small group of male homosexuals. The limitations and complications of such therapy prompt this report in spite of the small number of cases treated.

With one exception all the subjects were overt homosexuals who applied for treatment for various reasons. Four subjects accepted organotherapy by compulsion—that of a court order in the case of *G.W.*, and by the parents of the three adolescent homosexuals *R.R.*, *A.D.2*, and *F.G.* The other seven subjects sought treatment because of a desire to live heterosexually—some for social or economic advantages and others because of a desire to marry. One was a typical bisexual who preferred a heterosexual role.

Subjects *A.D.2* and *M.M.* presented the somatic pattern of eunuchoidism; *G.T.* and *J.M.* were of somewhat feminine configuration; the others fell into more or less average male patterns. The clinical observations other than that of sex-hormonal ratios were not remarkable.

METHOD

Eleven male subjects ranging in age from 16 to 34, who presented themselves for treatment of alleged homosexuality, were subjected to diagnostic study. Clinical observation included the determination of estrogens and androgens in the urine. The estrogens were assayed by a modification of the Allen-Doisy method using spayed rats. The androgens were determined by both biologic and colorimetric methods in seven subjects and by colorimetric method alone in four subjects. The biologic determination was carried out by modification of the Gallagher and Koch (1) method using white capons. The 17-ketosteroids were determined colorimetrically by the method of Callow (2). The estrogens are recorded in international units (I.U.), the androgens in capon unitage (C.U.) and the 17-ketosteroids (17-K) in milligrams. No attempt was made to convert the 17-K values into a biologic equivalent by the formula of Callow (2). The comparison of the 17-K and capon unitage in the subjects of another study[1] yielded a correlation of .58, a value which sets a limited validity to such conversion.

The range of values of urinary estrogens and androgens in normal adult males previously determined and partially reported in a previous communication (3) was: (a) estrogens, 25 to 50 I.U.; (b) androgens, 20 to 38 C.U.; (c) 17-ketosteroids, 18 to 42 mg. per 24 hours, respectively.

The urinary hormonal values of the 11 subjects under treatment are set forth in table 1. The "A" data represent values in all subjects before treatment; the "B" data those obtained in seven subjects after treatment.

The analysis of the data reveals the findings which in our experience (3) are usual in male homosexuality. Similar criteria were reported by Myerson and Neustadt (4). It is apparent that the estrogenic values are in general higher

[1] Unpublished data.

TABLE 1. SEX-HORMONE ASSAYS

Name	Age	Estrogens I.U. A	Estrogens I.U. B	17-Ketosteroids mg. A	17-Ketosteroids mg. B	Capon unitage A	Capon unitage B	Sex Behaviour
F.G.	(V) 21	50		16.1				Bisexual
M.B.	(V) 26	200	125	28.7	24.1	32	28	Passive Reciprocal
G.V.	(C) 28	25	25	20	29.2	12	18	Reciprocal Adynamic[2]
M.M.	(P) 20	25	25	19	5.8	12		Passive Reciprocal
S.H.	(V) 27	50	100		28.1	38	10	Reciprocal
S.M.	(V) 23	50		23.9		0		Reciprocal
G.T.	(V) 34	20	50	10.6	32.9	0		Passive Adynamic
J.M.	(V) 23	50		23.9		0		Passive Reciprocal
H.D.	(P) 17	25		9.1				Passive Reciprocal
R.R.	(P) 16	100	50	7.4	19.9			Reciprocal
A.D.	(V) 21	250 100[1]	50	9.5 17.8[1]	9.8			Adynamic (not overtly) homosexual

V—voluntary case
C—custiodal case
P—parental request

A—before therapy
B—after therapy
[1] Assay after second course therapy.

[2] Adynamic implies homosexual with somatic inferiority

and the androgens are lower than those of normals previously determined. The values of subject *G.V.*, however, may be considered normal. He presented himself as a custodial case for further treatment having already been treated intensively elsewhere. This previous therapy may have modified his sex-hormone chemistry but because homosexuality was still present he was given another course of treatment. The other cases had received no organotherapy previously. The organotherapy prescribed was patterned somewhat after that suggested by Wright (5). This consisted of testosterone proprionate[2] combined with chorionic gonadotropin.[3] Methyl testosterone was also administered as a supplement in six cases. Treatment was given usually twice weekly for periods varying from three to 24 months. The over-all details of the medication are summarized in table 2.

RESULTS

Treatment led to the following results. Insofar as homosexuality is concerned, organotherapy failed to influence the psychosexual behavior in eight of the subjects but seemed to benefit the other three. Of the latter, subject *F.G.*, who was a typical bisexual, reported predominantly heterosexual behavior without any homosexual trend or fantasy for eight months during therapy and for six months thereafter.

Subject *A.D.* who presented a striking adynamic, eunuchoid build associated with the highest titer of estrogens in this group responded favorably. Although not overtly homosexual he was troubled with homosexual fantasies. Following organotherapy these fantasies disappeared and a much needed increase

TABLE 2. ORGANOTHERAPY AND RESULTS

Name	T.P. (mg.)	M.T. (mg.)	P.U.(I.U.)	Duration (mos.)	Results
F.G.	650	2000	12000	8	good
M.B.	1000		8000	20	failure
G.V.	550		3000	3	failure
M.M.	250	1500	5000	5	failure
S.H.	1050		7500	13	failure
S.M.	350	2000	8000	5	failure
G.T.	1250	2750	16000	4	failure
J.M.		3500	6500	7	failure
H.D.	250	1550	7500	5	failure
R.R.	900	5500	18000	15	good
A.D.	1375		25500	7	good

T.P.: Testosterone Proprionate
M.T.: Methyl Testosterone
P.U.: Chorionic Gonadotropin

[2] Oreton, kindly supplied by the Schering Corporation.
[3] "A.P.L." kindly supplied by Ayerst, McKenna & Harrison.

in weight and energy was experienced. After eight months of treatment there was a sharp reduction in the estrogen titer from 250 I.U. to 50 I.U. but without any significant change in the 17-K values. Urinary assay again six months later, during intermission of treatment, revealed an increase in estrogens but a more significant rise in 17-K values. Subject *R.R.* seems to have achieved a satisfactory adjustment. He has "a steady girl friend" and no longer indulges in homosexual practices.

In view of the fact that these studies were not controlled by the use of placebos it is not possible to state the role that suggestion may have played in those cases which responded favorably to treatment. Those, however, who have attempted the difficult feat of treating homosexuality by psychotherapy alone will perhaps be most impressed with the positive results that were obtained.

Among the eight who failed to respond favorably subjects *M.B.*, *G.V.*, *S.H.*, *J.M.* and *H.D.* complained of an actual intensification of the homosexual drive so that further treatment was withheld or abandoned by them. In view of the antecedent hopes of the subjects, any influence that suggestion might have had in their cases would presumably have been in the direction of alleviation rather than accentuation of their homosexuality.

DISCUSSION

Much has been written about the nature of homosexual behavior, great stress being placed on the character of the role played by the subject. With this we quite concur if attention is given not only to which has the penile role but also which is the more active in the solicitation or whether there is mutuality in desire and whether heterosexual behavior is also present.

Any discussion of homosexuality demands consideration of the remarkable paper published by Kinsey (6) in 1941. This article is notable for the volume of data presented. Kinsey reported that "homosexuality" is a highly relative term and that the condition may occur in any combination and in any sequence with heterosexuality. In view of this intergradation he casts doubt upon the pragmatic meaningfulness of either term. It is to be noted, however, that if intergradation were to be thought of as vitiating classification the medical sciences would require revolution. In actuality, intergradation commonly reveals merely the concurrent operation of several factors and not the lack of validity of any one. It seems obvious that sexual behavior is a resultant of the operation of both hormonal and social factors. These, too, can appear in any sequence or combination, promoting now heterosexual and now homosexual reactions.

It may be further remarked that Kinsey underestimated the weight of the statistical evidence for the hormonal factor in the etiology of male homosexuality in Glass, Deuel and Wright's report (3) by using an inappropriate method of comparison based on his erroneous assumption that the relationship was a rectilinear one. Since the relationship is strongly curvilinear as may be observed from the graph, the appropriate device should be the frequency ratio method by which the ratio of the two categories is compared for the different magnitudes.

Using this method there is a ratio of homosexuals to normals of 1.00 below the median of the combined group at an a/e ratio of $7\frac{1}{3}$ with a ratio of only .26 above this critical point, which is definitely significant.

However, as Kinsey prefers to use the homosexual analyses separately rather than as case averages the corresponding calculation gives a median of combined group at 6.6 with a ratio of 2.8 below the median and .81 above it, which is also amply significant.

This much difference is found in spite of the fact that some of the determinations were based on colorimetric tests of all the 17-ketosteroids rather than biological determination.

The criticism based on variability of the samples does show the existence of important interfering factors, but when these differences are found in spite of such factors the hormonal factor is certainly present.

In relating our results to earlier reports such as that of Wright (5), which show higher percentages of success, it must be noted how few custodial cases there are in the present series. When the patient is in custody or under parole his opportunities for homosexual behavior and incitation thereto are reduced. He also has a strong impulse either to deceive the physician or at least to show a bias in his statements. In the patient who is not under control there is also a counter-activity of homosexual companions who drill into him the saying "once a homosexual, always a homosexual" together with a well practiced "line" of persuasion.

Inasmuch as treatment actually intensifies

the homosexual urge in some subjects it is well to note Terman's (7) observation that the active homosexual scores higher in masculinity in the masculine-feminine questionnaire test than normal males whereas the passive homosexuals go further in the female direction than do normal females. Moreover, Glass and Fields (8) have found that the Terman M-F score shows a substantial correlation with androgen production, *i.e.*, a fairly constant gradient above and below the base line. This means that the more active homosexual drive is associated with high androgen output as well as high positive M-F test results. Passive homosexuality was found to correlate with low androgen output and high negative M-F scores.

The fundamental fact in the present connection is that the primary effect of androgen is a generalized augmentation of susceptibility to sexual arousal and only secondarily do qualitatively different effects appropriate to the given sex appear (9). It would therefore be expected that the administration of androgen to the active (or aggressive) homosexual would rather regularly intensify his sex drive while that of the passive homosexual would also often be increased. Yet it is not enough to think of active and passive cases alone for there were eight reciprocal cases in our series. The category of reciprocals doubtless includes cases who are preferentially active or passive and perform the other role as a less preferred one or one which is merely accomodational. We plead for a more thorough investigation of the pattern and the environment in future cases when hormone studies are to be correlated. It is also desirable that all cases be measured with Terman or Guilford tests of masculinity-femininity along with the usual biologic measurements.

Another consideration in the problem of organotherapy in homosexuality is the essential substitutional character of the treatment, and especially in the adult subject. The adynamic hyposexual male can undoubtedly benefit insofar as his general somatic inferiority is concerned. It is probable that when his low androgen titer is raised and the associated excess estrogens suppressed by androgenic therapy he will be stimulated to a more normal sexual behavior. Likewise the juvenile homosexuals, especially those with hypogonadism, may be expected to respond favorably to combined androgenic-gonadotropic therapy. This may explain Lurie's (10) successful results in four such cases. Here sexual development and differentiation may yet be incomplete and judicious organotherapy may normalize the psychosexual pattern by promoting maturation. These hypogonadal subjects are more vulnerable to homosexual influence than normal males. Long continued therapy with high-dosage androgen of the adult seems actually to suppress seminal function even if suitably buffered with gonadotropin. This has been observed by one of us and reported by others as well who are treating infertile males (11, 12). Also to be noted is the irregular response to therapy as regards the sex-hormone ratio in the present series; estrogens and androgens may be increased in some cases and suppressed in others.

To anticipate a selective response from gonadotropic therapy, namely a stimulation of androgens alone without a corresponding effect on the estrogens in the male, seems unwarranted from the meager evidence at hand. Not enough is known of the influence of gonadotropins on the human gonadal function to warrant such an assumption. It may be of interest in this connection to note that subject *A.D.* showed an increased excretion of both estrogen and 17-ketosteroid after his second course of therapy.

The organotherapy of homosexuality has not reached a stage where one may simply administer androgens and gonadotropins to all cases with confidence of success. The fact is that sometimes instead of helping one gets a worsening of the condition. This might well have been expected in view of Terman's studies showing important differences between active and passive cases.

What is needed are restudies of the situation in which the nature of the patterns is analyzed, classified and the correlation to other psychosomatic determinations made in addition to the usual clinical evaluations of organotherapy. The final results will mean a larger percentage of benefit and a reduction of harm from this therapy. The results in appropriate cases are too good to permit undue pessimism as to the value of this treatment.

SUMMARY AND CONCLUSIONS

Eleven male homosexuals were subjected to trials with organotherapy to observe whether the administration of testosterone buffered with chorionic gonadotropin for periods varying from 3 to 24 months could favorably influence their psychosexual behavior. Only three of the subjects reported benefit from this therapy. Five reported an intensification of the homosexual drive. The influence of the treatment on the urinary excretion of estrogens and androgens was irregular, in that both increased and decreased hormone excretion was observed in different subjects.

The need for restudy of such treatment on a more comprehensive basis and the more careful selection of subjects for therapeutic trials is discussed.

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Endocrine Diseases as Revealed by 13,000,000 Examinations of Registrants

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AS MUCH AS possible should be learned statistically about the incidence and geographic distribution of disease. There exists at the present time an unusual and perhaps a unique opportunity. Some 13,000,000 examinations of registrants were made prior to January, 1944. These records have been assembled under one roof and may be subjected to statistical analysis at will. These 13,000,000 examinations have been conducted by well qualified physicians. The diagnoses, as a rule, are above the general average of medical examinations in accuracy. In fact, many of the records cover dual examinations: first, at the hands of the Selective Service examining physicians, and later, of those at the induction stations. In addition, at the induction stations many medically trained eyes thoroughly inspect every registrant. The quality of the record, therefore, is good as clinical records go.

To date only limited analyses have been attempted on random and selected samples of varying sizes and distribution, and then, as a rule, only as to incidence of certain diseases and the rejection rates at local boards and at the Armed Forces Induction Stations. To date three surveys have been completed, the results being published in Medical Statistics Bulletins Nos. 1, 2, and 3.

NOMENCLATURE AND CODES IN MEDICAL STATISTICS

Some of the difficulties attending statistical analyses of clinical records arise in the nature of original entries. Rubrics are set up within predetermined frames, e.g., disease of the kidney with subheadings, nephritis, albuminuria, etc.; or general heading—endocrine disease, with subheadings diabetes mellitus, glycosuria, etc. Thus, entries by physicians may indicate albuminuria, without determining its significance; others make a definite diagnosis and record as nephritis or Bright's disease. Likewise, in endocrine diseases, some examiners indicate glycosuria without indicating its significance; others label it diabetes mellitus, sugar diabetes, etc. For the guidance of coders, groups of equivalents or synonyms had to be set up. In doing so the effort was made to designate what was actually recorded, i.e., to leave albuminuria and glycosuria as such, unless other recorded evidence or statements indicated the presence of more serious disease, i.e., nephritis in one instance and diabetes mellitus in the other. When the diagnosis is definitely recorded as diabetes mellitus, it is probably correct. Further study is needed, however, to determine the significance of glycosuria—and particularly as to whether or not it represents potential and future diabetes.[2]

HEIGHT AND WEIGHT IN RELATION TO INDUCTION

The average height of all registrants was 5 feet, 8½ inches; the average weight was 152 pounds. The average height of the Negro registrant fell 2/5 inch short of that of the white and his weight was 1½ pounds less.

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[1] Chief, Medical Division, National Headquarters, Selective Service System; Vice-Chairman, National Committee on Physical Fitness, Federal Security Agency.

[2] Figures on endocrine disturbances do not include glycosuria except where specifically stated.

The military requirements on height and weight are fixed—based on experience. The lower limit for height is 5 feet and that for weight, 105 pounds. Men below these standards rarely have the strength to carry military equipment, etc. The upper limit of acceptance is 6 feet, 6 inches though the Navy limits them to 6 feet, 4 inches since above this height heads are constantly being bumped.

The height-weight relationship is shown in the accompanying three dimensional chart; the weight to height, subject to induction, is indicated in table 1.

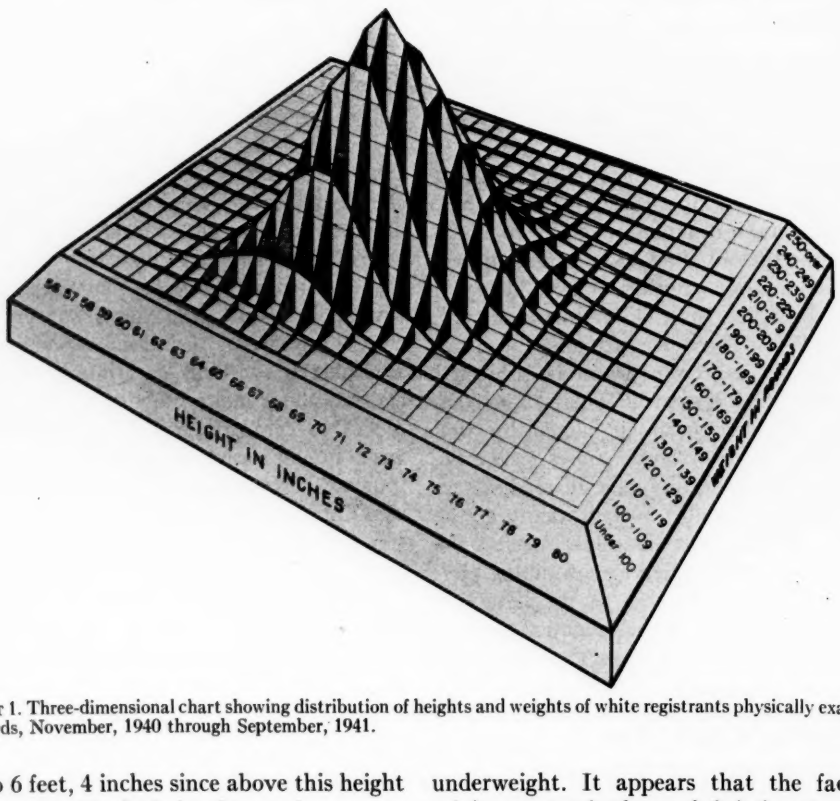

CHART 1. Three-dimensional chart showing distribution of heights and weights of white registrants physically examined at local boards, November, 1940 through September, 1941.

TABLE 1. INCIDENCE OF HEIGHT AND WEIGHT DEVIATIONS PER 1,000 REGISTRANTS EXAMINED

Bulletin No. 3	White and Negro	White	Negro
Underheight	0.7	0.7	0.5
Overheight	0.1	0.2	0.1
Underweight	14.8	17.3	6.8
Overweight	32.7	38.8	13.2

Based on data for November-December 1943.

The incidence of height and weight disqualifications per 1000 registrants examined are as shown in table 2.

Some generalizations are possible. Apparently underheight is much more frequent than overheight, *i.e.* at the rate of 7 to 1. Overweight, however, is more frequently disqualifying than underweight. It appears that the fact that minimum standards are definitely set and that maximums are left to the judgment of the examiners may result in more registrants being rejected for overweight.

Endocrine anomalies play a very considerable role relative to height and also to weight of individuals. Just what proportion of those disqualified in these fields are the victims of endocrine disease has not yet been determined. It offers, however, a valuable mass of data for future study and analyses.

When we come to the analyses of specific endocrine and allied diseases, the breakdown is rather coarse. But the analyses do reveal certain numerical relationships—the relative fre

quency of diabetes mellitus, of Fröhlich's disease[3] and of hyperthyroidism.

DIABETES MELLITUS

Glycosuria was relatively common—2.4 per 1,000 in the first survey, 1.1 in the second, and 1.5 in the third which represents wartime selection. However, true diabetes was 3.0 and 2.9 per 1,000 in peacetime, 1.6 in wartime. This difference can probably be best explained on the basis of manpower demand and supply. During peacetime the standards were high, all questionable cases being rejected for the simple reason that abundant manpower was available and strictly normal men were abundant. However, in wartime, selection was more exact; the manpower pool was undergoing rapid depletion; more careful investigation was made of registrants with definite glycosuria; less significance was attached to traces of sugar in the urine; and in only a trifle more than 50 percent of the instances was glycosuria considered to indicate true diabetes mellitus.

However, the IV-F pool shows the total rejections to date, May 1, 1944. The Class IV-F pool as of May 1 indicates 38,800 registrants in Class IV-F for endocrine defects or 1.0 per cent of all rejected registrants. This figure does not include those registrants in Class IV-F for underweight, overweight and height defects. Underweight and overweight account for an additional 60,700 Class IV-F registrants or 1.5 percent of the registrants in that class.

TABLE 2. PER CENT DISTRIBUTION OF ENDOCRINE REJECTIONS BY RACE

	Total	White	Negro
Total Endocrine	100.0	100.0	100.0
Diabetes mellitus	41.2	41.3	40.0
Fröhlich's syndrome[1]	23.8	23.9	23.5
Thyroid disturbances	19.7	19.6	19.4
Other endocrine disturbances	15.3	15.2	17.1

[1] In Mobilization Regulations, 1-9 Frölich's syndrome is listed under "Endocrine and metabolic diseases." The issue of the true etiology of the disorder is not raised at this juncture.

[3] See footnote Table 2.

TABLE 3. ESTIMATED PRINCIPAL CAUSES FOR REJECTION OF REGISTRANTS 18–37 YEARS OF AGE IN CLASS IV-F, AS OF MAY 1, 1944
(Preliminary)

Principal cause for rejection	Number	Percent
Total	4,049,000	100.0
Manifestly disqualifying defects	425,700	10.5
Mental disease	657,100	16.2
Mental deficiency[1]	563,300	13.9
Physical defects	2,345,200	58.0
Musculoskeletal	303,500	7.5
Syphilis	286,800	7.1
Cardiovascular	261,600	6.5
Hernia	229,000	5.7
Neurological	208,600	5.1
Eyes	206,100	5.1
Ears	156,100	3.9
Tuberculosis	107,700	2.7
Lungs	69,600	1.7
Underweight and overweight	60,700	1.5
Feet	51,700	1.3
Abdominal viscera	50,600	1.2
Kidney and urinary	41,900	1.0
Varicose veins	40,700	1.0
Genitalia	40,400	1.0
Endocrine	38,800	1.0
Teeth	35,800	0.9
Skin	24,900	0.6
Neoplasms	24,900	0.6
Nose	24,300	0.6
Gonorrhea and other venereal diseases	18,200	0.4
Hemorrhoids	16,500	0.4
Mouth and gums	11,000	0.3
Infectious and parasitic	4,200	0.1
Throat	4,000	0.1
Blood and blood-forming	3,800	0.1
Other medical defects	23,800	0.6
Non-medical defects	57,700	1.4

[1] Includes registrants rejected for educational deficiency before June 1, 1943 and for failure to meet minimum intelligence standards after that date, as well as those rejected for mental deficiency.

DISEASES OF THE THYROID

The same pattern obtains in thyroid disease relative to the significance of clinical findings. During peacetime all doubtful cases were considered significant with the result that the incidence was 5.0 per 1,000 but, as manpower for the fighting forces was becoming scarce, only the more outstanding clinical pictures were labelled actual disease a fact which resulted in an incidence of 0.6 per 1,000. Hyperthyroidism, both in war and peace, was more frequent than hypothyroidism.

PITUITARY DISEASE

Some insight concerning the role of the pituitary in growth and development is reflected in the figures for height and weight. However, specific figures are available for Fröhlich's syn-

drome and also for gigantism and acromegaly. Fröhlich's disease was diagnosed in 1.8 per 1,000 examined in the first survey; in 2.4 in the second survey during peacetime, and in 1.9 per 1,000 in the third survey which represents wartime selection. Hyperactivity of the pituitary was much less frequent. Gigantism or acromegaly yielded figures of 0.4, 0.2 and less than 0.1 per thousand respectively in the three surveys.

TABLE 4. COMPARISON OF INCIDENCE OF ENDOCRINE DISTURBANCES IN PEACETIME AND WARTIME IN RATES PER 1,000 EXAMINED

Disease	Through May 1941	Through September 1941	November and December 1943
Total	18.4	20.8	7.1
Frölich's syndrome	1.8	2.4	1.9
Acromegaly and gigantism	0.4	0.2	[1]
Hyperthyroidism	3.9	4.0	0.5
Hypothyroidism (Myxedema and Cretinism)	0.8	1.0	0.1
Diabetes mellitus	3.0	2.9	1.6
Glycosuria	2.4	1.1	1.5
Other Endocrine	6.1	8.5	1.3

[1] Less than 0.1 per 1,000.

Simple goiter was found to be present in 4.1 registrants per 1,000 in peacetime and 0.3 per 1,000 in wartime.

Wartime selection apparently reduced the diagnosis of endocrine disease, especially thyroid disease and diabetes. In the earliest peacetime data, 5.4 per 1,000 showed sugar while later in peacetime this figure dropped to 4.0 and then to 3.1 per 1,000 in wartime.

It is worthy of note that: (1) endocrine disease rates relatively high as a cause for rejection—1% of the total rejected; (2) Fröhlich's disease is more frequent than gigantism and acromegaly combined; and (3) hyperthyroidism occurred 4 to 5 times as often as hypothyroidism.

From this it appears that in the examination of men for the fighting forces Fröhlich's syndrome and diabetes mellitus stand out preeminently in the endocrine field. Wartime selection was more searching in character. Examiners when faced with endocrine manifestations made relatively fewer positive diagnoses of endocrine disease during wartime than in times of peace.

SUMMARY

From Selective Service statistical studies to date, some pertinent facts are emerging. Endocrine diseases are relatively frequent. These diseases (including Fröhlich's syndrome) occupy 16th place in the IV-F pool as it is composed at present. This represents in round figures 38,800 cases, or 1% of the rejections. Pressure for manpower limits making endocrine diagnoses in wartime as contrasted with peacetime—much that is merely suggestive of endocrine dyscrasias is discounted when rejection is involved as the result of a positive diagnosis. Diabetes mellitus and Fröhlich's syndrome stand out preeminently among endocrine diseases as reflected in the examination of registrants for service with the armed forces. Only about 50% of those with glycosuria are considered to be suffering from diabetes. Rejections involving endocrine disease totalled 38,800 and those involving underweight and overweight totaled 60,700. When time permits, there will be available for analysis a valuable pool of records in the field of endocrine diseases. Plans for recheck studies of rejections and for the best interpretation of statistics should be made at this time.

ASSOCIATION NOTICES

ANNOUNCEMENT OF ANNUAL MEETING

The Twenty-Eighth Annual Meeting of The Association for the Study of Internal Secretions will be held in New York City on Monday and Tuesday, June 18–19, 1945. The Hotel Commodore will be headquarters for registration and for the scientific and business sessions. Room reservations should be made directly with the hotel of your choice. Because of previous commitments, The Commodore requests that all our members plan on releasing their rooms on Tuesday afternoon, the 19th. Therefore, if you plan on remaining in New York beyond that date, it is suggested that reservations be made elsewhere. May we urge you to MAKE YOUR HOTEL AND TRANSPORTATION RESERVATIONS IMMEDIATELY and avoid disappointment, remembering you may cancel if you find you are unable to attend.

At the 1944 meeting, it was voted that the next annual meeting be held in connection with the American Medical Association. However, in late November, the A.M.A. officials decided to move their meeting from New York to Philadelphia. Upon investigation, it was found that accommodations in the latter city were so inadequate that your Council voted to hold the meeting in New York. Because of the proximity of the two cities and lack of hotel space in Philadelphia, many physicians will have reservations in New York and commute to the A. M. A.

The Chairman of the Local Committee is Dr. Earl T. Engle, 630 West 168th Street, New York City, assisted by Dr. Robert Gaunt, New York University, who will be in charge of projection arrangements.

PRESENTATION OF PAPERS

1. The title of the paper and four copies of a comprehensive abstract should reach the President, Dr. Carl R. Moore, Department of Zoology, University of Chicago, Chicago 37, Illinois, not later than March 15, 1945.

Abstracts submitted should be in proper form for printing in the program. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have their titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the Program Committee and the final program announced about May 10, 1945.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of ENDOCRINOLOGY or THE JOURNAL OF CLINICAL ENDOCRINOLOGY. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the Annual Meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. Fred C. Koch (Chairman), Department of Biochemistry, University of Chicago, Chicago, Illinois.

Dr. George W. Thorn, Peter Bent Brigham Hospital, Boston, Massachusetts.

Dr. Willard M. Allen, 630 South Kingshighway Blvd., St. Louis, Missouri.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the Chairman, Dr. Fred C. Koch, before March 15, 1945.

The terms of the following officers expire at the time of the Annual Meeting in New York in 1945:

President-Elect	Fuller Albright
Vice-President	W. O. Thompson
Secretary-Treasurer	Henry H. Turner

Council Members

E. L. Sevringhaus R. G. Hoskins Earl T. Engle

CARL R. MOORE, *President*
HENRY H. TURNER, *Secretary*

NOMINATIONS FOR AWARDS OF THE ASSOCIATION

Two Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. The work may be either clinical or in the basic sciences. A special Committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council.

Each member of the Association has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of his most important papers with reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, *not later than March 15, 1945*. The Awards are described below.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, in 1942 to Dr. Fred C. Koch, and in 1944 to Dr. Edward A. Doisy. No age or other special limitation is stipulated by the Donor of the Award. So far it has been given for long-continued work of a high quality.

THE CIBA AWARD

The Ciba Award was established in 1942 and is to be given to an investigator not over 35 years of age. No recipient was selected in 1942. In 1944 the Award was given to Dr. E. B. Astwood. The Award is for $1,200.00. If the recipient chooses to use the Award to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

CARL R. MOORE, President
HENRY H. TURNER, Secretary

LETTER

TESTS FOR PREGNANCY

To The Editor

In reading the editorial in the August issue of your Journal in which rapid tests for pregnancy were discussed, it seemed to us that certain considerations which, during fourteen years of experience, we have come to consider important, were overlooked.

In the first place, we have for many years substituted serum for urine as the material to be tested. Unextracted urine is frequently toxic, but this objection is less serious than the chances for error introduced by the fact that even morning specimens vary tremendously in their degree of concentration. The amount of hormone excreted in 24 hours is uninfluenced by the volume of urine excreted. Unless some measure of the concentration is made, therefore, the use of 10 cc. of one specimen may be testing for five to ten times as much hormone as would be tested for in the use of 10 cc. of another specimen. This consideration makes it necessary to know what part of a 24-hour volume a given specimen represents and to concentrate dilute specimens. Many methods for concentrating chorionic gonadotrophin in urine have been carefully tested in this laboratory. Our conclusion has been that, because of the marked variations in the constituents, the pH, and the concentration of different specimens, the recovery, by any method, is inconsistent and quite unsatisfactory. All of these objections are overcome by the use of serum, which is uniform in its concentration and from which chorionic gonadotrophin may consistently be quantitatively recovered by the classical Ascheim-Zondek technic, *i.e.*, alcohol precipitation. It was at least ten years ago, while making quantitative determinations of the levels of chorionic gonadotrophin in the urine and serum of toxemic versus normally pregnant women, that we discovered that falsely negative tests were occasionally encountered in urine specimens but almost never when serum was used.

In the second place, the possibility of getting a falsely positive test because of the presence of a high level of pituitary gonadotrophin should be emphasized. We are particularly aware of this in our laboratory because of the fact that tests are never performed merely to satisfy the curiosity of an essentially normal woman, but only in cases in which it is clinically important to know whether or not a patient is pregnant. In such cases the pituitary factor is quite likely to be high. In the five-day rat test a pituitary F.S.H. reaction may usually be readily distinguished from the grossly visible discrete corpora lutea that result from chorionic-gonadotrophin administration. The 18-hour rabbit test, however, depends only upon the rupture of follicles, a reaction which is given by both the pituitary and chorionic hormones. The same objection, so far as we know, applies to the use of the rapid development of ovarian hyperemia of the ovary of the rat as a test object. Whether or not the frog test is more specific has yet to be established. Guterman's recently proposed test for pregnanediol is appealing because it avoids this source of error. It, however, is open to the objection that falsely negative results would be expected since pregnanediol excretion in early pregnancy is frequently no higher than in the non-pregnant woman.

As a result of the above considerations we always use serum rather than urine and the five-day rat test rather than the more rapid but less specific test reactions. It has seemed to us that the greatest possible accuracy is more important, from both the clinical and the psychological aspects, than speed. Except for the diagnosis of ectopic pregnancy, we know of no situation in which any danger to the patient would be involved in waiting five days for the result. And, if an ectopic pregnancy is suspected, clinical judgment is the only criterion upon which it is safe to rely.

Finally, it is not sufficiently recognized by most practitioners that the pregnancy test—whatever method is used—is not infallible. It is quite possible to have an ectopic pregnancy or a missed abortion without any viable chorionic tissue—and hence no chorionic hormone. We have even had a number of cases of mole and one of chorioepithelioma in which the concentration of chorionic gonadotrophin was far below that of normal pregnancy, and a few normally pregnant women upon whom we have never been able to get a positive A.Z. test. There is also in our records a case of abnormal bleeding and lower-abdominal pain three months after a miscarriage. The titer for chorionic gonadotrophin in the serum was very high—she was excreting some pregnanediol and a goodly amount of estrogen. Operation revealed retained products of a completely benign nature. These cases are cited in order to demonstrate that clinical judgment should not be unduly influenced by the results of a test for pregnancy. Because of the wide variations encountered in both normal and abnormal situations, no hormone assays, however accurate, can ever be in the same category as tests for N.P.N. in the blood or sugar in the urine. A failure to recognize this fact leads to the performance of a pregnancy test in many instances when none is indicated, to unnecessary delay and to considerable confusion when the answer is not what would be expected clinically.

O. Watkins Smith
George Van S. Smith

Fearing Research Laboratory
Free Hospital for Women
245 Pond Avenue, Brookline 46
Massachusetts
October 31, 1944

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. D. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, AND HAROLD WOOSTER.

BOOK REVIEW

WEISMAN, A. L., AND C. W. COATES

The South African frog (*Xenopus laevis*) in pregnancy diagnosis. New York Biologic Research Foundation, New York, 1944.

The use of the African-frog test for pregnancy was introduced by Shapiro and Zwarenstein in 1933 and about the same time by Bellerby, only two years after the publication of the better-known Ascheim-Zondek test. In the interval the use of the frog test has extended widely, having been promoted in the United States especially by Weisman and Coates.

These same authors now offer in monographic form an interesting review of the whole subject. The work is written in the spirit of the naturalist but with adequate attention to the practical medical aspects, also. The classification, ecology, anatomy and behavior of *Xenopus* are first discussed, then special phases of its physiology—and especially reproductive physiology—are treated. The major emphasis of the book, however, is upon the reactions of the frogs to various hormones and especially to pregnancy urine. The technical minutiae of the pregnancy test are detailed in such fashion as to facilitate the clinical use of the method. Other practical items are the care and breeding of the frogs as well as their diseases. Accompanying the monograph is a supplement—something in the nature of a catechism—designed to guide beginners in the use of the test.

The authors are obviously fascinated with their subject and succeed in passing on considerable of the fascination to the reader.—*R.G.H.*

ADRENALS

BRUGER, M., J. A. ROSENKRANTZ AND B. E. LOWENSTEIN

Studies on the morphology of the adrenal cortex and on the excretion of 17-ketosteroids in hypertensive patients. *Am. J. Med. Sci.* 208: 212. 1944.

The authors reviewed the clinical and necropsy records of 135 patients, and classified 65 as hypertensives because two or more of the following criteria were present: 1) persistent systolic blood pressure of 140 mm. Hg. or more; 2) persistent diastolic blood pressure of 90 mm. Hg or more; 3) width of the left ventricular wall exceeding 12 mm. (in the absence of rheumatic or luetic heart disease, and of hyperthyroidism); 4) increased total heart weight and 5) arteriolar sclerosis. Hyperplastic or adenomatous changes in the adrenal cortex were found in 30 (46%) of the hypertensive group and in 33 (47%) of the normotensive group. As a second part of the study the authors determined on single 24-hour specimens the 17-ketosteroid excretion by 40 hypertensive women ranging in age from 28 to 70 years with an average systolic blood pressure of 200 mm. Hg (range 150–274) and an average diastolic blood pressure of 110 mm. Hg. (range 80 to 148), and by 14 normotensive women ranging in age from 20 to 76 years. Women were selected because in them the entire 17-ketosteroid output appears to derived from the adrenal cortex. The urinary 17-ketosteroid excretion values were between 2.5 and 12.5 mg./24 hr. in 37 of the hypertensive and in 4 of the normotensive subjects, and between 12.5 and 22.0 mg./24 hr. in 3 of the hypertensive and in 10 of the normotensive women. The hypertensive patients averaged 14.2 $\pm$4.0 mg.; the normotensive 8.4$\pm$4.3 mg./24 hr. All of the differences between the two groups in the second part of the study were statistically significant. The authors conclude that: 1) hypertension is not necessarily accompanied by any specific alteration in the histology of the adrenal cortex, and 2) the evidence from this study does not preclude the possibility of adreno-cortical hyperactivity in patients with hypertension since the amount of urinary cortin-like substances was not determined. However, if it can

be demonstrated that the adrenal cortex of hypertensives does not produce an excess of cortin, they postulate that their studies on 17-ketosteroid excretion suggest a hypofunctioning adrenal cortex in patients with hypertension, reflecting perhaps a gland exhausted under the constant strain imposed upon it by the persistent elevation in blood pressure.—*E.C.R., Jr.*

D'Angelo Rodriguez, A.

The antiuremic and renotropic action of steroid hormones. Selye's method. *Semana méd:* 51, I: 1062. 1944.

A total of 11 patients with urea values in the serum from 53 to 235 mg. per cent were treated with desoxycorticosterone acetate using intramuscular injections of 2 to 5 mg daily. No selection of the patients with reference to ailment was attempted and neither history nor diagnosis are given. A definite reduction in the blood uera was obtained in every case. The arterial pressure did not rise; on the contrary, a moderate reduction was observed in some cases. The treatment is void of danger if the patient is carefully observed.—*A.E.M.*

Hopper, J., Jr., A. W. Winkler and J. R. Elkinton

Simultaneous measurements of the blood volume in man and dog by means of Evans blue dye, T1824, and by means of carbon dioxide. II. Under abnormal conditions, including secondary shock. *J. Clin. Investigation* 23: 636. 1944.

Data of endocrine interest comprise only a portion of this paper. Two patients with treated Addison's disease; dogs following dehydration with and without salt depletion, and dogs in which adrenalectomy had been performed were among the subjects of the study. Results with both methods of determining blood and plasma volume probably gave figures that were slightly higher than the actual, but this error was too small to interfere with their clinical usefulness. Data obtained by the dye and the gas were comparable under all the conditions tested except in certain cases of shock due to acute salt depletion, in which the dye failed to record a decline in blood volume that the investigators had reason to believe existed.—*T.H.McG.*

Marangoni, B. A., and V. C. D'Agati

Hepatorenal failure in the Waterhouse-Friderichsen syndrome. Clinico-pathologic observations in two cases with prolonged survival periods. *Am. J. Med. Sci.* 207: 385. 1944.

The authors report two cases which survived 80 and 88 hours respectively. Because of these prolonged survival periods, hitherto unrecognized, clinical and pathological features were observed. The former were characterized by renal failure, the latter by the hepatic necrosis and renal glomerular and tubular changes usually found in the hepatorenal syndrome. The authors conclude that: 1) there are two stages in the Waterhouse-Friderichsen syndrome—A. a first stage, usually resulting in death from fulminating shock and toxemia, and B. a second (hepatorenal) stage, wherein death ensues from hepatorenal failure; 2) life expectancy in the syndrome is inversely proportional to the degree of adrenal tissue destroyed by hemorrhage; and 3) accepted modes of therapy (sulfadiazine, meningococcus antitoxin, desoxycorticosterone, adrenal cortical hormone plasma and other fluids) may have prolonged the clinical course but did not alter the fatal outcome in these cases. They postulate that the following sequence of events occurs: 1) patient receives fulminating profound meningococcus infection; 2) adrenal glands are destroyed by hemorrhage with loss of their detoxification activities; 3) liver, with function depressed by shock and toxemia, is too overwhelmed to meet detoxification requirements, 4) as a result, liver undergoes toxic necrosis, elaborates a potent tissue toxin, and floods the circulatory system with it and with unneutralized bacterial toxins; 5) kidneys attempt to excrete these harmful products through the proximal convoluted tubules and develop degenerative changes in these tubules, glomerular changes of the nephritic type, and diminished renal blood flow with avascular glomerular tufts; and 6) patient succumbs from renal failure.—*E.C.R., Jr.*

McLetchie, N. G. B.

Adrenal virilism. Report of a case with unusual features. *Brit. J. Surg.* 32: 90. 1944.

A case of virilism is described. The condition developed at puberty in an apparently normal female child. While male characteristics developed to a striking degree, the patient menstruated in the latter part of her life. Death occurred at the age of 40 years from peritonitis. At autopsy, the following abnormalities were found. (1) The right adrenal cortex was thickened and there was ectopic adrenocortical tissue in the region of the coeliac axis; both tissues had been reduced by a chronic obliterative process. These

were considered to be the essential abnormalities determining the condition of virilism, and their reduction the factor which allowed the development of menstruation and explained the finding of a large corpus luteum in the right ovary and a thick endometrium at autopsy despite the striking male facies and habitus. (2) Mammary carcinoma with hepatic metastasis; bilateral ovarian dermoid cysts, epithelioma arising in the wall of the right dermoid and infiltrating the colon, with production of peritonitis. The problem of the interrelationship of all these abnormalities is discussed. Attention is drawn to other conditions which may give rise to masculinization in the female.—*Author's Summary.*

ENDOCRINE GENERAL

BAYLES, T. B., AND C. B. RIDDELL

Plasma lipids in patients with rheumatoid arthritis receiving gold salt therapy and during pregnancy. *Am. J. Med. Sci.* 208: 343. 1944.

The authors recall the fact that jaundice and pregnancy cause a marked amelioration in the manifestations of rheumatoid arthritis. In an effort to find an explanation, they have studied the plasma lipids of 21 patients with active rheumatoid arthritis (10 with non-specific therapy and 11 with added gold salt therapy) and of 4 pregnant rheumatoid arthritics (3 prepartum and postpartum, and 1 during pregnancy). They conclude: 1) in patients with active rheumatoid arthritis the plasma lipids as determined (total lipid, total cholesterol, and phospholipid content) and as calculated (total fatty acids, total phospholipid, phospholipid fatty acid, cholesterol ester fatty acid, neutral fatty acid, neutral fat and lipid ratios) are normal; 2) these constituents show very little change during gold salt therapy; 3) lipemia of pregnancy patients with active rheumatoid arthritis is qualitatively and quantitatively similar to that of normal subjects; and 4) the ameliorative effect of pregnancy in rheumatoid arthritis is not dependent on any alterations in the plasma lipid constituents.—*E.C.R., Jr.*

BENJAMIN, H.

The new concept of gerontotherapy. *Urol. & Cut. Rev.* 48: 17. 1944.

The author points out that the ageing process leads to organ deficiencies and cell deficiencies in which the endocrine structures share. An illustrative case is cited by way of making the point that hormones in small dosage and supplemented by vitamines are commonly conducive to increased efficiency and well being of the ageing person. The dosages should be kept at a level to promote the nutrition of, rather than unduly to stimulate, the generally weakening tissues. In case of thyroid a dosage of one-fourth grain a day or less is favored. Androgen in the form of testosterone propionate injections should be used ordinarily in dosage of 5 or 10 mg. twice weekly, in which dosage only "tonic" but not erotic effects are induced.—*R.G.H.*

CHARNY, C. W.

The use of equine gonadotropin in male infertility. *Am. J. Med. Sci.* 207: 519. 1944.

The author reviews his results in 127 unselected cases treated with equine gonadotropin (Anteron-Schering) intravenously. The usual dosage was 400 international units 3 times weekly for 3 to 6 months. The arbitrary criterion for cure was an increase in the total spermatozoa count to at least 200 million; an increase in the spermatozoa count of more than 1 million which failed to give a total count of 200 million was classed as improvement. Of the 127 cases, 12 (9%) were "cured," 22 (17%) were "improved," and 93 (74%) remained unchanged.

The cases were classified before treatment on the basis of the findings in a testicular biopsy. The histologic pictures of 4 types of pathologic findings are described: I, complete atrophy; II, severe degenerative changes; III, moderate degenerative changes; and IV, combinations of groups I, II, and III. In this classification the following assumptions are made: 1) the size of the tubules is an index of the stage at which development ceased and degeneration set in, 2) the presence of peritubular fibrosis is indicative of a longstanding pathologic process, and 3) there is apparently an increase in the amount of normal interstitial tissues (but not necessarily in the interstitial cells of Leydig) in instances of clear-cut endocrine underdevelopment. The correlation between the biopsy and semen findings was not constant. In the 93 patients in whom repeated semen examination revealed no improvement after therapy, 48 (52%) of the preliminary biopsies were classified as having histologically irreparable lesions, while 45 (48%) were considered to have histologically reparable lesions. Re-biopsy after treatment in 4 of the former group showed no growth in germinative epithelium; re-biopsy after treatment in 15 of the latter

group showed epithelial growth (limited to multiplication of the younger cell forms) in 11 (73%). The author pointed out that the failure to obtain an equally large percentage of "cures" in the 45 patients with seminiferous tubules which could conceivably regenerate may be the result either of insufficient potency of the administered gonadotropin or of the lack of a maturation factor therein. He concluded that: 1) equine gonadotropin has therapeutic value in selected cases; and 2) testicular biopsy is of considerable value in prognosticating which cases of male infertility will respond to this therapy.—*E.C.R., Jr.*

DYER, W. W.

Masked hypoglycemia. *Pennsylvania M. J.* 47: 1210. 1944.

This is a short, useful discourse on the subject, with 3 illustrative case histories. There are probably many cases of spontaneous hypoglycemia masquerading as epilepsy, psychoneurosis, neurasthenia, menopausal neurosis, etc. The diagnosis in these patients can be established by a relatively simple and common laboratory procedure if care is taken to insist upon a normal diet preceding the tolerance test and to insist upon a 5-hour examination rather than the conventional 3-hour test. Complete study of a patient must be made as well as the glucose tolerance test. After the diagnosis is established, many of these patients respond to a simple dietary regime and appropriate treatment of the attendant disease, if any exists. Failure to respond calls for further study and diagnostic research.—*I.B.*

FARRIS, E. J.

Validity of two-hour rat test for human pregnancy. *Am. J. Obst. & Gynec.* 48: 200. 1944.

Over 360 urine specimens were tested on more than 1,000 immature female albino rats for color reaction, to determine pregnancy and non-pregnancy conditions. At least, two female rats (ages to 22 to 33 days, and weights 30 to 45 grams) were injected subcutaneously with 2 cubic centimeters of the urine specimen. The ovaries were examined at the desired time. The positive ones had a definite blush to strong red color; the negative ones were uniformly pale. In 61 subjects, the 2, 6 and 24 hour tests were all in agreement with the Friedman test. In 11 patients with menopausal symptoms, the 2 hour test was positive in each instance, but this reaction often faded to negative in the 6 and 24 hour tests. All patients were non-pregnant and the Friedman was negative in 10 of 11 patients. In other patients, it was noted that the 2 hour test was more sensitive, giving a positive reaction earlier in pregnancy than the Friedman.

In male patients, control specimens taken the morning of a scheduled evening coitus showed 4 positive and 8 negative responses. One hour before anticipated coitus, there were 5 positive and 1 negative reactions. The after-coitus urines showed 4 positive and 1 negative within an hour, 8 positive and 1 negative within 4 hours, and 6 positive and 5 negative within 11 hours. It was also shown that females have positive postcoital reactions. The author wonders whether or not it is possible that frequent coitus produces excess hormonal output in the female and upsets the normal hormonal balance, thereby explaining sterility in some childless couples who have frequent coitus.—*E.C.H.*

FINKLER, R. S.

Zondek's simplified treatment of secondary amenorrhea. *Am. J. Obst. & Gynec.* 48: 26. 1944.

Estradiol benzoate 2.5 milligrams and progesterone 12.5 milligrams were administered intramuscularly on two successive days to 31 patients with amenorrhea of 2 months to 7 years duration. In each instance, the cause of no bleeding was predicated to be ovarian or pituitary failure. Uterine bleeding resulted in 80.6 per cent of the patients after the first series of treatments. Bleeding started on the average of 4 to 6 days after the second injection. Pre-treatment and post-treatment biopsies indicated that no marked changes were produced in the endometrial pattern.—*E.C.H.*

GEOGHEGAN, F., AND J. MCGRATH

Experience with the Hogben test. *Irish J. Med. Sci.* 6th Ser. No. 225: 485. 1944.

The authors report upon their experiences with the *Xenopus laevis* test for pregnancy. The untreated urine was administered in 400 cases. The test was found to be "extremely poor," the "accuracy level" being less than 50%. One definitely false test was secured. The intra-individual variability of responsivity of the test animals proved to be fairly marked. Priming with chorionic gonadotropin did not prove to offer any advantage. It is planned to continue the work with extracted urine.—*R.G.H.*

GRAEF, I., J. NEGRIN, JR., AND I. H. PAGE

The development of hepatic cirrhosis in dogs after hypophysectomy. *Am. J. Path.* 20: 823. 1944.

Fatty cirrhosis of the liver was found in 5 dogs hypophysectomized 4.5 months to 3.75 years prior to postmortem examination. Hypothalamic lesions were found in these animals, the damage being proportional to the degree of cirrhosis. There was general obesity and marked increase of weight in the cirrhotic dogs. Other hypophysectomized animals without hypothalamic injury, however, became obese. The thymus had failed to involute in some animals and in others was hyperplastic. In 4 of the 5 cirrhotic dogs there was congestion of the spleen with atrophy of the red and white pulp. There was no significant correlation between the occurrence of diabetes insipidus and associated hypothalamic changes.—*R.C.*

HART, B. F., W. T. MCCONNELL AND A. N. PICKETT

Vitamin and endocrine therapy in nausea and vomiting of pregnancy. *Am. J. Obst. & Gynec.* 48: 251. 1944.

Forty-three patients with vomiting of early pregnancy received pyridoxine hydrochloride in doses of 50 to 100 milligrams daily and intravenously. Of these, 25 were primigravidas and about 75 per cent was relieved completely; 18 were multigravidas, only 33 per cent was ameliorated.

Sixty-six similar patients received combined doses of thiamine hydrochloride and pyridoxine hydrochloride in daily oral doses from 50 to 100 milligrams of each. Of 39 primipara, about 80 per cent was relieved completely; of 27 multipara, about 55 per cent stopped vomiting.

Five patients who were not benefited by this latter therapy were given adrenal cortical extract, usually 2 cubic centimeters subcutaneously daily. Three were able to retain food.—*E.C.H.*

JONES, G. M.

Diabetes insipidus. Clinical observations in forty-two cases. *Arch. Int. Med.* 74: 81. 1944.

This is a very useful historical and etiological survey of the subject, with valuable clinical data on 42 cases. This contribution does not lend itself to abstracting but should be studied in its entirety. On the basis of the report of important features in 42 cases of diabetes insipidus, in 34 of which the etiologic factors were clinically or pathologically determined, it is pointed out that diabetes insipidus is a symptom complex produced by injury to the supraopticohypophysial tract, and not a specific etiologic entity. In any case of diabetes insipidus thorough and repeated examinations should be made to determine the etiologic factors. Urine concentration tests indicate that patients with diabetes insipidus receiving a limited intake of fluid continue to secrete urine of low specific gravity, with resultant loss of body weight. In any case in which such a response is obtained the diagnosis or organic damage along the supraopticohypophysial tract should be made. Ideally, therapy in any case of diabetes insipidus should be directed toward the etiologic factor. Thus, in some cases of neoplasm of the hypothalamus and pituitary and of Hand-Schüller-Christian disease a good response to roentgen irradiation is obtained, and antisyphilitic therapy corrects the diabetes insipidus resulting from syphilis. As diabetes insipidus is not infrequently the first symptom in cases of neoplasm, occurring 8 months and 6 years respectively before other evidence of the malignant growth in 2 of the cases reported here, roentgen irradiation of the hypothalamicohypophysial region may well be worth while when the cause of the diabetes is undetermined. Of the various methods of administration of posterior pituitary as replacement therapy in the absence of the antidiuretic principle, intramuscular injection of pitressin tannate in oil seems the most desirable at present. Intranasal application of pitressin in jelly was the least satisfactory of the methods tried. Use of a low salt diet as an adjunct to other therapy may be worth a trial in any case of diabetes insipidus. Thyroidectomy should not be performed for diabetes insipidus unless there are other specific indications for the procedure.—*I.B.*

KUPPERMAN, H. S., P. FRIED AND L. Q. HAIR

The control of menorrhagia by prolactin. *Am. J. Obst. & Gynec.* 48: 228. 1944.

The lactogenic hormone was administered subcutaneously in dosages ranging from 100 to 250 International Units every day or every second day for one to eight days during episodes of menorrhagia of 43 women. Fifteen of 17 women, with functional menorrhagia, had satisfactory responses. Twenty of 23 women with menorrhagia associated with uterine fibromyomas gave satisfactory results. Six of 9 women

with menorrhagia associated with cystic ovaries responded adequately. Nine of 14 women with menorrhagia associated with chronic pelvic inflammatory disease were benefited. Eight of 14 were treated who had dysmenorrhea associated with menorrhagia were definitely improved. Three of 6 patients with threatened abortion had amelioration of symptoms and 3 aborted. Prolactin, when administered to normal cyclic women in doses of 300 to 500 International Units per week for periods of 7 to 10 weeks, did not have any appreciable effect upon the length of cycle, amount of bleeding or condition of the endometrium.—*E.C.H.*

LURIE, L. A.

The endocrine factor in homosexuality. Report of treatment of 4 cases with androgen hormone. *Am. J. Med. Sci.* 208: 176. 1944.

The author suggests that homosexuality be divided into: a) the acquired type, explained on the psychoanalytic basis as outlined by Freud and his disciples, and b) the innate type, explained on the basis of a somatic factor in the form of an endocrine disorder. He cites in detail the data on 4 cases to illustrate the latter type. These patients were adolescent males aged 13 to 22, with hypogonadal status (eunuchoid skeleton; delayed bone age; high-pitched voice; lack of beard; effeminate physical appearance, gait and mannerisms; small to large genitalia with a female hairline; decreased body hair) and with abnormal psychological reactions (marked feeling of inferiority and insecurity, compensated for by stealing or by neuroticism culminating in withdrawal from reality and by attempting suicide; and homosexual trends with or without overt sex perversion practices). In these patients the abnormal behavior and personality was thought to be due to emotional reactions to awareness of an organ deficiency. Treatment with 25 mg. of testosterone propionate intramuscularly three times a week for 3 to 6 months brought about structural and functional changes with disappearance of the hypogonadal status and the abnormal psychological reactions, and with development of normal adult masculine physical characteristics, attitudes and trends. The need of the somatopsychic approach to the understanding of these cases is stressed.—*E.C.R., Jr.*

MOORE, O.

Correspondence to the Editor. *Am. J. Obst. & Gynec.* 48: 282. 1944.

The writer suggests the use of the noun "agenesis" and the adjective "agennetic" when one is concerned with women who have borne no children.—*E.C.N.*

PECK, F. B., AND C. V. SAGE

Diabetes mellitus associated with Albright's syndrome (osteitis fibrosa disseminata, areas of skin pigmentation, and endocrine dysfunction with precocious puberty in females). *Am. J. Med. Sci.* 208: 35. 1944.

The authors report the first known case of these conditions in association. Insulin resistance and unresponsiveness to hypoglycemia were demonstrated by the insulin tolerance test. The authors suggest that these abnormalities in carbohydrate metabolism in this patient may indicate a complex endocrine disturbance, possibly originating before birth, and implicating the pituitary gland.—*E.C.R., Jr.*

SMITH, O. W., G. V. S. SMITH AND D. HURWITZ

The relationship between hormonal abnormalities and accidents of late pregnancy in diabetic women. *Am. J. Med. Sci.* 208: 25. 1944.

In 16 pregnant diabetic women the authors have measured the serum chorionic gonadotropin at 1- to 2-week intervals starting between the 16th and 29th weeks; and in 8 of them they have determined the total amount of urinary estrogenic activity before and after zinc hydrolysis starting at the same period during gestation. Of the 16 women, only 8 had normal offspring, and in all but 3 there occurred some accident of late pregnancy (mild toxemia, eclampsia, preeclampsia, premature delivery, intra-uterine death, or neo-natal death). Of the 8 in whom estrogen excretion studies were made, only 1 had a normal pregnancy. At least 10 weeks prior to the clinical accident there was an increased excretion of estrogen coincident with a decreased amount of additional estrogenic activity following zinc hydrolysis. The authors interpret this to indicate increased estrogen production and decreased estrogen degradation (hence increased progestin production). This was followed by a decrease in total estrogen excretion and an increase in the additional estrogenic activity after zinc hydrolysis, which they interpret to indicate decreased estrogen production and increased estrogen degradation (hence decreased progestin production). This increase of estrogen and progestin followed by a decrease of both hormones has been shown by the authors to be the normal pattern occurring just prior to menstruation and only after the

36th week of gestation preceding normal labor. The premature appearance of this pattern preceded by 5 weeks any rise in the serum chorionic gonadotropin (which did not always occur). The authors concluded that the fundamental deviation from the normal in these cases was the premature ripening of the placenta with ensuing premature senility which may be accompanied by a secondary rise in the serum chorionic gonadotropin level. The rationale of estrogen administration as preventive therapy in these cases is discussed.—*E.C.R., Jr.*

SONTAG, L. W., E. L. REYNOLDS and V. TORBET

Status of infant at birth as related to basal metabolism of mother during pregnancy. *Am. J. Obst. & Gynec.* 48: 208. 1944.

Basal metabolic rates of 163 women in the last month of pregnancy, as well as data of the gain in basal metabolic rate during the course of gestation, are presented. The weight, length and skeletal development of the infants were recorded at birth and at one, three and six months. Infants of mothers with a high basal metabolic rate during the ninth month were heavier and longer at birth and more advanced skeletally at one month than infants of mothers with low basal metabolic rates during the last month of pregnancy. Infants of mothers in the second group tended to gain faster in weight, height and ossification during the first six months than did those of the first group.

The same relationship was found in comparing the infants of mothers with a high basal metabolic rate gain during pregnancy with those of the low gain group, except that at six months the gain in ossification slightly favored the high group.—*E.C.H.*

WISHNOFSKY, M., A. P. KANE AND C. S. BYRON

The influence of pituitrin and epinephrine on the action of insulin on blood sugar. *Am. J. Med. Sci.* 208: 361. 1944.

The authors have examined the question of whether pituitrin and epinephrine counteract the action of insulin on the blood sugar level. The general procedure was to perform a 2-hour oral dextrose tolerance test in 5 to 10 diabetic patients whose insulin had been withdrawn for a standard period of time, and to compare each patient with himself by repeating the test 2 days later under identical conditions except for the addition of injections of the drugs in question. The following regimes were compared: a) dextrose alone with dextrose plus pituitrin subcutaneously (s.c.); b) dextrose and insulin s.c. with dextrose and insulin s.c. plus pituitrin s.c.; c) dextrose and insulin intravenously (i.v.) with dextrose and insulin i.v. plus pituitrin i.v.; d) dextrose and insulin s.c. with dextrose and insulin s.c. plus epinephrine s.c.; and e) dextrose and insulin i.v. with dextrose and insulin i.v. plus epinephrine s.c. The following conclusions concerning the blood sugar level of diabetic patients receiving dextrose were reached: 1) pituitrin s.c. alone had no effect on it; 2) insulin s.c. or i.v. lowered it; 3) pituitrin s.c. definitely counteracted the effect of insulin s.c.; 4) pituitrin s.c. had not the slightest effect on the action of insulin i.v.; and 5) epinephrine s.c. markedly antagonized the action of insulin whether given s.c. or i.v. To explain the contrasting effect of pituitrin on the action of insulin s.c. and of insulin i.v. the theory has been advanced that pituitrin, by virtue of its vasoconstrictor action, retards the absorption of insulin given subcutaneously and, in this manner, prevents insulin from acting on the blood sugar. To test this theory, the authors determined the excretion of phenolsulfonphthalein (P.S.P.) s.c. in 6 normal individuals with and without pituitrin s.c. Since the absorption of P.S.P. injected s.c. was not influenced by pituitrin s.c., the authors contend that this theory is untenable to explain the mechanism by which pituitrin counteracts the action of insulin s.c. on the blood sugar level. The mechanism remains unexplained. Partial neutralization of the action of 15 units of insulin s.c. was obtained with 20 units of pitruitin s.c. Since the dose of pituitrin employed is far in excess of that used clinically, the neutralization is of physiologic interest only, and need not be taken into consideration in determining insulin dosage in diabetics who are receiving pituitrin simultaneously.—*E.C.R., Jr.*

ZWARENSTEIN, H. AND D. G. DUNCAN

Ten years of the Xenopus pregnancy test. *Clinical Proceedings* 3: 186. 1944.

The technique of the Xenopus pregnancy test on urine and blood, and the technique of the dilution test for hydatidiform mole and chorionepithelioma are described. Thirty-one per cent of 1,407 complete pregnancy tests performed during the period September, 1933 to September, 1943 was controlled by subsequent clinical diagnosis. In 98.6 per cent of these cases the laboratory diagnosis was correct. Eleven cases of suspected

hydatidiform mole and chorion-epithelioma were controlled by subsequent clinical or pathological findings. Of these 8 were correct positives (3 cases of hydatidiform mole, 4 cases of chorion-epithelioma and 1 case of chorio-adenoma), 2 correct negatives and 1 incorrect positive. The last proved to be a case of twin pregnancy.—*Author's Summary.*

GONADS

AUSTIN, B. R. AND G. W. RAMSEY

Brenner tumor of the ovary associated with sarcomatous change in fibromyomata uteri. *Am. J. Obst. & Gynec.* 48: 263. 1944.

The authors report a patient who had a Brenner Tumor of the ovary that was quite typical clinically and pathologically. It was unusual only in that it was associated with a fibromyoma of the uterus which showed sarcomatous degeneration.—*E.C.H.*

BICKERS, W.

A study of the endometrial pattern before and after treatment for amenorrhea. *Am. J. Obst. & Gynec.* 48: 58. 1944.

Seven patients with no bleeding for 5 months or more, in whom persistent proliferative endometriums were found on weekly pretreatment biopsies, were treated with diethylstilbestrol, 5 milligrams daily for 10 days. This was supplemented by 5 milligrams of progesterone intramuscularly daily during the last 5 days. Uterine bleeding occurred in 6 patients within 4 days after cessation of treatment. Endometrial biopsies of 6 patients were taken and no marked alterations were seen in the endometrial patterns as a result of therapy. The six patients who bled were given another similar course of therapy from the fifteenth to the twenty-fifth day of after bleeding. Five of these had withdrawal bleeding and continued to bleed fairly regularly for periods of 3 to 12 months.

Two patients with amenorrhea of 5 and 14 months' duration had persistent secretory endometriums. Operation discovered persistent corpora lutea. The first patient had menses on the third postoperative day and she has been cyclic since. The second patient bled on the second postoperative day, had cyclic menses and became pregnant 8 months later.—*E.C.H.*

HANDLEY, MAJOR R. S. AND MAJOR T. CRAWFORD

Polyorchidism. *Brit. J. Surg.* 31: 300. 1944.

The presence of three testes in an apparently normal male is reported. The extra testis was on the right side and was small but of perfect architecture. It showed spermatogenesis. The cases of polyorchidism reported in the literature are reviewed briefly and the characteristic features of this rare condition summarized.—*D.P.*

HARDING, F. E.

Oral substitution therapy with ethinyl estradiol and alpha estradiol. *Am. J. Obst. & Gynec.* 48: 181. 1944.

Ethinyl estradiol and alpha-estradiol were given orally to 47 and 80 patients, respectively, with varying degrees of hypoestrogenism. Evaluation was on the basis of subjective responses. The author believes that ethinyl estradiol is the most potent oral estrogen available at present. A satisfactory relief of hypo-ovarian symptoms was obtained usually with 0.05 to 0.1 milligrams daily.—*E.C.H.*

HUEPER, W. C.

Seminoma in the testis of a dog. *Am. J. Clin. Path.* 14: 418. 1944.

A seminoma of the Sertoli cells of the testis of a dog was found and described. The cells resembled those of the hyperplastic Sertoli cells in human testes after roentgen treatment and atrophy. There were no significant findings in the other organs related to the neoplasia with the possible exception of the prostate which was characterized by a definite glandular hyperplasia.—*R.C.*

KUZMA, J. F., AND O. R. LILLIE

Primary ovarian pregnancy. *Am. J. Obst. & Gynec.* 48: 268. 1944.

Three cases of primary ovarian pregnancy are briefly reported. All are authentic according to the classification of Spiegelberg. None had previously conceived. Fertilization was thought to have occurred within the follicle in two cases and implantation in an endometrial implant apparently accounts for the other.—*E.C.H.*

LEVAN, A., AND P. B. SZANTO

The frequency of anovulatory menstruation as determined by endometrial biopsy. *Am. J. Obst. & Gynec.* 48: 75. 1944.

Two hundred and sixty-one endometrial biopsies were taken the last one-third of the menstrual cycle from 103 patients in a mental

hospital. Sixty-seven women had 3 endometrial biopsies each; 24, two biopsies; and 13, one biopsy. Nonsecretory endometriums were found 14 times in 9 women. Two patients had 3 consecutive nonsecretory endometriums. One patient had 2 anovulatory cycles out of 3. Six patients had one anovulatory cycle; 5 of these had 3 biopsies each and one 2 biopsies. The incidence of anovulatory cycles was 5.36 per cent. The patient incidence was 8.7 per cent.—*E.C.H.*

McGAVACK, T. H.

The implantation of compressed pellets of α-estradiol benzoate and α-estradiol in the treatment of the female climacterium: Preliminary report. *Bull. New York Med. Coll.*, Flower and Fifth Ave. Hospitals. 7: 40. 1944.

Five patients with menopausal symptoms, in one of whom a surgical menopause and kraurosis vulvae existed, have been successfully treated with alpha-estradiol benzoate and alpha-estradiol pellets implanted subcutaneously. Periods of relief following the implantation of from 15 to 30 mg. of alpha-estradiol benzoate have varied from 56 to 210 days. Periods of relief following the implantation of 10 and 20 mg. of alpha-estradiol have varied from 164 to 186 days. Early, the absorption per 15 mg. pellet of alpha estradiol benzoate may reach 0.065 mg. daily, while later it may average as little as 0.037 mg. daily. Advantages and disadvantages of the method are discussed.—*D.A.M.*

McGRATH, E. J., AND L. G. HERRMANN

Influence of estrogens on the peripheral vasomotor mechanism. *Ann. Surg.* 120: 607. 1944.

The experimental background for the clinical use of estrogenic substances in the treatment of peripheral vascular disease is presented. A series of 345 patients, so treated over the past ten years is presented, and the results analyzed. In all these patients vasomotor disturbances played either a primary or at least a major secondary role. The results of these clinical studies indicate, we believe, that in estrogenic substances, we have a powerful therapeutic agent for the treatment of peripheral vascular disturbances in which there is a significant component of vasomotor imbalance.—*Author's Summary.*

MENDEL, E. B., AND C. TYRONE

Thecoma of the ovary with ascites and hydrothorax (Meigs' syndrome). *Am. J. Obst. & Gynec.* 48: 271. 1944.

The authors report a patient with a thecoma of the ovary associated with ascites and hydrothorax. Both the latter appeared during a two weeks, observation period and approximately one gallon of amber colored fluid was found in the peritoneal cavity at operation. The patient had no complaints nine months after operative removal of the tumor.—*E.C.H.*

MULLIGAN, R. M.

Feminization in male dogs. A syndrome associated with carcinoma of the testis and mimicked by the administration of estrogens. *Am. J. Path.* 20: 865. 1944.

Dogs given stilbestrol for 129 to 291 days in total amounts of 330 to 2985 mg. developed characteristics similar to those of dogs with carcinoma of the testis. There was general loss of hair, and libido, after 500 mg. intake, was greatly depressed; the breasts were prominent; the penile sheath swollen, the prepuce enlarged and testes reduced in size. The histology of the endocrine glands is described and the authors cite references to articles about dogs with carcinoma of the testis presenting similar characteristics.—*R.C.*

RINSKY, ABRAHAM

Spectacular response of a patient with cancer of the prostate to estrogen treatment. *Semana méd:* 51, I: 601. 1944.

The 52 year old patient had a history of prostatic ailment of 3 years. The diagnosis was established by biopsy. During the first 20 months the course was mild, although with many remissions, the conditions gradually becoming worse. During the following 14 months the patient was confined to bed with extreme constipation, urinary difficulties, leg edema and intense pain especially in the tibias. Daily injections of 50,000 units of estrogen brought about improvement within 5 days so that morphine could be omitted. Within 12 days all difficulties had disappeared except the osseous pains. Cessation of treatment was followed by a relapse within 3 or 4 weeks. Vitamin B given at that time was without benefit. The estrogen treatment was resumed for 35 days. As a result the patient appeared to be practically cured except for a certain debility.—*A.E.M.*

ROBERTS, H. K., E. B. HELWIG, R. ELMAN AND C. M. MACBRYDE

Serial biopsy studies of the effects of estrogens

on the liver. *J. Clin. & Lab. Med.* 29: 1062. 1944.

Eight dogs were divided into four groups, one receiving 5 mg. of diethylstilboestrol dipropionate in 1 cc. of olive oil daily for 17 days; a second, the olive oil alone for a like period; the third, 1.66 mg. of alpha estradiol dipropionate in 1 cc. of sesame oil daily for 16 days; and the fourth, the sesame oil alone. Hepatic fat, glycogen, and nitrogen were determined chemically and histologically by biopsy during "control" and "test" periods and finally in autopsied material. There was no significant alteration as a result of the administration of either the natural or the synthetic estrogen, although thrombocytopenia had been produced in each animal prior to sacrificing. The histologic estimation of the amount of hepatic fat afforded only a rough correlation with the chemical analyses.—*T.H.McG.*

SWEENEY, BEATRICE M.

The effect of estrone on anaerobic glycolysis of the uterus of the rat in vitro. *J. Lab. & Clin. Med.* 29: 957. 1944.

Uterine tissues taken from white rats spayed at the age of three months were subjected to the action of estrone in bicarbonate Ringer's solution through a range of dilutions from 0.001 to 5 micrograms per one cc. Glycolysis proceeded equally in all preparations and at a rate similar to that obtained for control tissues suspended in the bicarbonate Ringer's solution alone. This is in sharp contrast to the increased production of lactic acid seen following the injection in vivo of estrone into the uteri of spayed rats. The author believed some essential accessory factor was missing in the in vitro experiment. The rate of glycolysis was not influenced by the further addition of succinate, malate, indole-acetic acid or standard chorionic gonadotropin to the in vitro preparation.—*T.H.McG.*

WATTS, R. M., AND F. L. ADAIR

On the chemistry of ovarian cysts. *Am. J. Obst. & Gynec.* 48: 1. 1944.

Determinations of sodium, potassium, chloride, nitrogen, non-protein nitrogen, protein, glucose, total solids, water, ash and specific gravity were made on 29 ovarian cyst fluids from 15 ovarian tumors (9 benign and 6 malignant) and three fluids from parovarian cysts. Values vary greatly among the fluids of different cavities of the same tumor as well as among the fluids of different types of cysts. In general, cysts with actively secreting epithelium and a cellular basal layer contain fluids high in potassium, nitrogen and protein and low in chloride, those with less actively secreting epithelium and an evascular or hyalinized basal layer contain fluids low in potassium, nitrogen and protein and high in chloride.—*E.C.H.*

HYPOPHYSIS

BELINKOFF, S.

Cyclopropane—Pituitrin incompatibility. *Am. J. Obst. & Gynec.* 48: 109. 1944.

It is pointed out that the combined use of cyclopropane and pituitrin is fraught with danger because they are both parasympathetic stimulants. Two reports are given of fatalities probably resulting from this incompatibility. The authors make a plea for the use of pitocin, the oxytoxic fraction, which does not have the side effects of pituitrin, or for the use of ergonovine.—*E.C.H.*

HICKEY, R. C., AND K. HARE

The renal excretion of chloride and water in diabetes insipidus. *J. Clin. Investigation* 23: 768. 1944.

In previous studies, there was a consistently different renal response to the administration of hypertonic saline solutions in normal dogs as compared with those having diabetes insipidus. By means of inulin clearances and estimations of blood and urine chloride, the concentration of chloride in the reabsorbate from the glomerular filtrate was brought into relationship with the concentration of chloride in the blood. In the normal animal this reabsorbate-plasma (R/P) ratio rose sharply when water was given by mouth or hypotonic saline solution was injected intravenously, and decreased progressively when hypertonic solution was administered. However, in diabetes insipidus, the R/P was initially greater than one and usually increased during the infusion of hypertonic saline solution. The addition of pituitrin in large amounts restored this response to normal. On the basis of these facts the R/P was determined in normal and in three polyuric subjects during the infusion of hypotonic, isotonic and hypertonic solutions, respectively. Two of the latter subjects had a known disturbance of the hypothalamico-hypophyseal system, while the third was primarily polydypsic. In response to test the first two behaved like dogs with diabetes insipidus, whereas the response of the last mentioned was identical

with that of the normal subject. It was concluded that the liberation of the antidiuretic hormone from the neurohypophysis in response to the injection of hypertonic sodium chloride provides a means of testing the functional capacity of the gland. The inhibition by salt injection of a pre-existing water diuresis was thought to be good evidence that the hypothalamico-hypophyseal system was functioning satisfactorily; a continuation or increase in the high rate of flow was indicative of a polyuria of pituitary origin.—*T.H.McG.*

ROBERTIS, E. DE, AND E. DEL CONTE

A cytological method for the determination of the thyrotropic pituitary hormone: *Rev. Soc. Argentina Biol.* 20: 88. 1944.

Young guinea pigs were injected with graded doses of the thyrotropic preparation and frozen sections of the thyroids made after 30 minutes. The "cytological coefficient" is defined as the ratio between the number of colloid droplets $\times 100$ and the average diameter of the follicles. The coefficient increases in proportion with the logarithm of the dose. The unit is defined as the quantity of hormone able to quadruple the cytological coefficient. This unit is about 1000 times smaller than the Junkmann-Schoeller unit. The method can be used as an assay of organic fluids from normal and pathologic persons.—*A.E.M.*

ZECKWER, I. T.

Correlation of the alterations in mammary glands, pituitary body and ovaries of parabiotic rats. *Arch. Path.* 38: 99. 1944.

The pituitary gland of a gonadectomized rat in parabiosis with an intact female secretes an increased amount of FSH which acts on the ovaries of the conjoined animal. Primarily there is an enlargement of the follicles and secretion of estrogen by the stimulated ovaries with little effect on the mammary gland. Subsequently there is release of the luteinizing hormone with resultant formation of corpora lutea in immature rats and enlargement of those present in mature rats, together with a hyperplasia of the mammary glands. In the next stage the follicles of the ovary continue to be stimulated and become cystic, the corpora lutea disintegrate, presumably because production of LH has been inhibited by the estrogen or the gland exhausted. Simultaneously there is active secretion of the hyperplastic mammary gland. In the fourth stage the corpora lutea all disappear and the ovary becomes composed of follicles and solid masses of granulosa cells. Copious mammary secretion continues and in some animals two types of adenoma develop. Pituitary cells become degranulated, enlarged and vascular, composed entirely of chromophobe cells.—*R.C.*

PANCREAS

BAILEY, O. T., C. C. BAILEY AND W. H. HAGAN

Alloxan diabetes in the rabbit. A consideration of the morphologic and physiologic changes. *Am. J. Med. Sci.* 208: 450. 1944.

The authors have studied the lesions produced in Dutch and Chinchilla rabbits by either: a) a single rapid injection of 200 mg. per kg. of alloxan, or b) the repeated injection of 40 mg. per kg. of alloxan over a period of 2 to 3 weeks. Animals were sacrificed or the pancreas of anesthetized rabbits was biopsied at suitable intervals so that the course of changes in the pancreas and other organs could be followed. The authors summarize their findings as follows: 1) the lesion in the islets of Langerhans begins almost immediately (within 5 minutes) after the injection of alloxan; 2) the islet lesion is degenerative from the beginning; 3) degenerative changes in the islet cells are already apparent in the initial hyperglycemic stages, and in the hypoglycemic stage they progress to a point where they approach those of the diabetic phase; 4) the histologic lesions in the different phases of the blood sugar curve are one continuous process; 5) the pancreatic acini remain normal throughout and changes in organs other than the pancreas are minimal; 6) alloxan has a specific action on the islet cells in which the beta cells are affected most severely but a certain percentage of the alpha cells remains intact; 7) the lack of cellular response to the necrosis in the islet cells of Langerhans is remarkable and presents a biologic problem of considerable interest from the standpoint of general pathology; 8) the number and variety of changes in the islet cells induced by small doses are not reminiscent of any well-known lesions of these islets but are somewhat suggestive of the early sequences in other organs following administration of certain carcinogenic hydrocarbons.—*E.C.R., Jr.*

BELL, H. G., L. GOLDMAN, LEELA S. CRAIG AND H. MCCORKLE

Hyperinsulinism. A report of the surgical treatment of three patients. *Surgery* 15: 681. 1944

Three cases of hyperinsulinism were reported

Symptoms suggesting hypoglycemia were present in all three and the minimum fasting blood sugar determinations were considerably below 50 mg. per cent. Solitary tumors of pancreatic islet cells were excised from the region of the tail of the pancreas in two of the patients. In one of these the tumor was almost completely extrapancreatic. In these two cases, operation was followed by relief of symptoms of hypoglycemia and return of the fasting blood sugar level to within normal limits. The third patient was known to have had diabetes mellitus for seven years. Episodes of hypoglycemia appeared and became progressively more frequent and severe over a period of a few weeks. At operation no evidence of tumor or aberrant pancreatic tissue could be found. A partial resection of the pancreas was performed. The condition of diabetes mellitus recurred following the operation and subsequently the patient has remained diabetic. Pathologic examination of the part of the pancrease excised showed alterations in the staining of the tissue suggesting the presence of islets of Langerhans that were increased in number and size.—*D.P.*

BRUNSCHWIG, A.

Survival of rhesus monkey four years after excision of head of pancreas with occlusion of external pancreatic secretion. *Surgery* 16: 416. 1944.

This is a report of the autopsy findings in a rhesus monkey which survived for four years following excision of the head of the pancreas and ligation of the neck of the organ. The autopsy revealed that the operation had been followed by permanent atrophy of the acinar tissue of the body of the pancreas. There had been no regeneration of acinar tissue or duct proliferation. Islet tissue survived and apparently functioned to permit normal carbohydrate metabolism as there had been no evidence of significant physiologic disturbances during the survival period. The significance of a four-year survival period in the absence of pancreatic acinar tissue and with absence of external pancreatic secretion is emphasized.—*D.P.*

THYROID

LANGE, K.

Capillary permeability in myxedema. *Am. J. Med. Sci.* 208: 5. 1944.

The author describes a method he has devised for the exact estimation of capillary permeability which employs the detection of the fluorescence of injected fluorescein with a photoelectric skin colorimeter. A standard curve based on 20 normal individuals is given; the value of these persons fell within a narrow range. Five cases of myxedema all showed a marked increase in capillary permeability which returned rapidly to normal with thyroid therapy simultaneously with a marked diuresis. Increased capillary permeability was present in two cases with edema due to undernutrition and severe avitaminosis but was absent in nine patients with cardiac edema and in three cases with edema of the legs from cirrhosis of the liver. Two of the myxedematous patients were studied with the electrocardiograph before and after thyroid therapy. The changes were attributed by the author partly to a change in capillary permeability and hence to a reduction in the interstitial edema of the heart muscle. A prolonged circulation time was found in all the cases of myxedema; this returned to normal with effective treatment.—*E.C.R., Jr.*

LAHEY, F. H.

The combination of Lugol's solution with thiouracil in the preoperative preparations of patients with toxic goiter. *Lahey Clin. Bull.* 4: 2. 1944.

In an informal note the author calls attention to the finding that patients treated before operation with thiouracil present thyroid glands that are somewhat friable and tend to ooze disconcertingly. When, however, Lugol's solution is given following the thiouracil the glands become firm, pale and non-friable. "The combination seems to be practically a complete answer to the problem."—*R.G.H.*

MCCLENDON, J. F., AND W. C. FOSTER

Protein-bound iodine in erythrocytes and plasma and elsewhere. *Am. J. Med. Sci.* 207: 549. 1944.

The authors have employed their own method (methanolacetone) of determining protein-bound iodine to the plasma and erythrocytes of man, dog, cow, horse, rabbit and cat. The results indicate that the determination of protein-bound iodine in plasma has no advantages over its determination in whole blood as the corpuscles contain about as high a concentration as plasma. —*E.C.R., Jr.*

MCINTOSH, C. B.

The treatment of hyperthyroidism in children. *J. Pediat.* 25: 133. 1944.

The author reviews the treatment of hyperthyroidism at the Iowa University Hospital since 1925. Of 23 children, 19 were subjected to subtotal thyroidectomy and 4 were treated without surgery. In the operated group there were 9 complete arrests, 3 nearly complete arrests, 5 recurrences, and 2 deaths; the average period of time for treatment was 6 weeks. Review of the literature indicates that with judicious use of iodine the operative mortality has dropped to 2.5 per cent. All of the unoperative cases were successfully treated by conservative management. In view of the present trend away from surgery in this disease, attention is called particularly to this group. All received more or less complete bed rest, phenobarbitol sedation, a high caloric and high carbohydrate diet. Three were given Lugol's solution; the fourth received no iodine. Roentgen ray therapy was used in two cases as an adjunct after medical treatment alone appeared to be inadequate. The average period of time for treatment of the four non-operated cases was seven months. A review of previous reports on the treatment of childhood thyrotoxicosis is presented and the use of roentgen therapy is discussed briefly. The author concludes that children deserve an adequate trial of medical management before surgery is advised and that in a considerable number of them surgery is neither necessary nor desirable.—*E.C.R., Jr.*

MOORE, F. D., D. N. SWEENY, JR., O. COPE, R. W. RAWSON AND J. H. MEANS

The use of thiouracil in the preparation of patients with hyperthyroidism for thyroidectomy. *Ann. Surg.* 120: 152. 1944.

Thiouracil was administered to 53 thyrotoxic patients as a preparation for thyroidectomy. This communication is a full report of the clinical and anatomic findings in the 34 of these patients who came to operation and were followed long enough for adequate study. Of these 34, 26 received thiouracil as the only preparatory drug. Control data were obtained from a study of 35 iodine-treated patients. The study revealed that thiouracil will bring the patient to operation with a normal metabolic rate, regardless of the degree of elevation of the rate prior to therapy. The lowering of the basal metabolic rate is accompanied by an intensification of the hyperplasia seen in thyrotoxicosis. The hyperplasia is accompanied by an increased vascularity and friability which makes the thyroid more difficult to handle and renders hemostasis arduous. The increased vascularity is especially troublesome if the patient has had a previous thyroidectomy. Preliminary or concomitant iodine administration delays the thiouracil response. It is suggested that iodine therapy subsequent to thiouracil treatment might serve to reduce hyperplasia and vascularity. The administration of thiouracil was sometimes followed by symptoms of toxicity not unlike that of the sulfonamides. Conclusions: Thiouracil is superior to iodine as a preparation for thyroidectomy. It is not yet the ideal drug for this purpose because (1) it increases the histologic abnormality of the disease, (2) it affects only the production of hormones and not the underlying etiology of the hyperthyroidism, (3) surgery may be rendered more difficult by it and (4) disturbing evidences of toxicity may become manifest following its administration.—*D.P.*

PICO ESTRADA, OCTAVIO, AND CALIXTO SIBILLA

Hyperthyroidism in children. *Semana méd.*, 50: 1357. 1943.

Hyperthyroidism in children is infrequent. Among the hyperthyroid cases in a large Argentine hospital only 1.6% were children. Although there are a few cases which resist treatment, the development is usually benign. The measures in children must be less radical than in adults. Medical treatment (iodine or diiodotyrosine) with physiotherapy leads frequently to cure.—*A.E.M.*

RADCLIFFE, C. E.

Observations in the relationship of the thyroid to the polyuria of experimental diabetes insipidus. *Endocrinol.*, 32: 415. 1943.

In cats with well established diabetes insipidus due to lesions of the hypothalamic-hypophyseal system, thyroid feeding produces an increased urine output which is associated with a positive shift in the chloride balance, i.e., a diminished chloride output, although a brief period of increased chloride excretion may follow the initiation of feeding. In normal animals the same influence on chloride excretion is observed, but there is no significant diuretic response. After thyroidectomy, the animals with diabetes insipidus had average volumes of urine which were 25 to 35 per cent less than during the previous period of polyuria, but these were still 3 to 4 times greater than the output of normal cats. The chloride excretion was affected but little after the immediate post-operative period of 1 or 2 days. Feeding thyroid to these animals had the usual effect as indicated above. Associated with thyroid feeding there is a net rise in the daily excretion of urinary

nitrogen of about 12 per cent in both normal cats and those with diabetes insipidus. The nitrogen excretion curve, however, does not parallel the curve of diuresis and the increased nitrogen excretion is probably only contributory to the mechanisms involved in the diuresis.—*Author's Summary.*

ROTH, G. M., R. D. WILLIAMS AND C. SHEARD

Skin temperatures of the extremities of persons with induced deficiencies of thiamine, riboflavin, and other components of the B complex. *J. Clin. Invest.*, 23: 373. 1944.

In connection with the general problem implied in the title of this paper, the authors have studied the effects of thiamine deficiency on induced hyperthyroidism. Thiamine was restricted to 0.45 gm. per 1000 calories of the daily diet, a limitation not sufficient of itself to produce unequivocal clinical signs of thiamine want. Simultaneously one subject was given 10 and the other, 8 grains of desiccated thyroid substance daily. At the end of 108 days, both subjects showed severe signs of thiamine deficiency. The basal metabolic rate had been increased to plus 19.1 per cent in one, and to plus 25.6 per cent in the other. Following this, the thiamine intake was gradually increased over a period of 77 days until as much as 15 gm. daily was being received by each subject, despite which definite evidence of thiamine deficiency still remained. "Apparently the thyroid hormone was less effective for the maintenance of metabolic processes in states of thiamine deficiency than in the normal state, for concomitantly with the increase of intake of thiamine, the basal metabolic rates became higher." No relationship between the vitamin deficiency and the skin temperatures could be established, but changes in the basal metabolic rate altered these temperatures during periods of vitamin B_1 depletion in a manner comparable to that seen in the hyperthyroid individual with an adequate vitamin intake.—*T.H.McG.*

SURE, B., AND Z. W. FORD, JR.

Influence of hyperthyroidism on urinary excretion of thiamin and riboflavin. *Endocrinol.*, 32: 433. 1943.

Subcutaneous injections of 0.5 to 1.0 mg. of synthetic thyroxin to adult albino rats for 17 to 21 days resulted in the excretion of large amounts of riboflavin in the urine. Since hyperthyroidism also produced large losses of body weight and of riboflavin from many of the tissues, the increased excretion of riboflavin in the urine may have been caused by body tissue catabolism. Hyperthyroidism, however, caused negligible changes in the level of thiamin in the urine and much smaller losses of this vitamin from the tissues.—*Author's Summary.*

TREUSCH, J. V., E. J. KEPLER, M. H. POWER AND S. F. HAINES

Creatinuria in hyperthyroidism and in essential hypertension, *Am. J. Med. Sci.* 208: 310. 1944.

Values for urinary creatine were determined in 39 cases of hyperthyroidism and in 35 cases of essential hypertension with or without an elevated basal metabolic rate. Of 29 patients with exopthalmic goiter, 20 (69%) excreted more than 135 mg. of creatine in 24 hours, 5 (17%) excreted 90 to 135 mg. and 4 (14%) excreted less than 90 mg. Of 10 patients with adenomatous goiter with hyperthyroidism, 6 (60%) excreted more than 135 mg. of creatine in 24 hours, 2 (20%) excreted from 90 to 135 mg. and 2 (20%) excreted less than 90 mg. The totals were fairly evenly divided between the sexes. Of 6 patients with adenomatous goiter without hyperthyroidism, 1 (17%) excreted more than 135 mg. of creatine in 24 hours, 5 (83%) excreted less than 90 mg. Of 18 hypertensive patients whose basal metabolic rates were plus 15% or more, 12 (66%) excreted less than 90 mg. of creatine per 24 hours, 3 (17%) excreted from 90 to 135 mg. and 3 (17%) excreted more than 135 mg. Similarly, of 17 hypertensive patients whose basal metabolic rates were less than plus 15%, 11 (65%) excreted less than 90 mg. of creatine per 24 hours, 5 (29%) excreted between 90 and 135 mg. and 1 (6%) excreted more than 135 mg. In summary, the majority of patients who had hyperthyroidism excreted more than 135 mg. of creatine in 24 hours, whereas the majority of patients who had essential hypertension even with an elevated basal metabolism excreted less than 90 mg. of creatine in 24 hours. The authors concluded: 1) the wide scattering of the results limited markedly the value of spontaneous creatinuria as a clincial sign for ruling hyperthyroidism in or out in cases of essential hypertension with elevated basal metabolism; 2) the results in general tended to substantiate the opinion that the elevated basal metabolism in essential hypertension rested on a different physiologic basis than that in hyperthyroidism.—*E.C.R., Jr.*

WILLIAMS, R. H., G. A. KAY AND B. J. JANDORF

Thiouracil. Its absorption, distribution, and excretion. *J. Clin. Investigation* 23: 613. 1944.

Knowledge concerning the absorption, distribution and excretion of thiouracil was gained by applying Grote's observation that a color developed when substances of the C=S type were treated with a special sodium nitroferricyanide reagent. Within 2 hours of ingestion, between 76 and 91 per cent of the drug was absorbed from or destroyed in the gastrointestinal tract. Although the amount destroyed in the gut could not be determined accurately, it was believed to be less than 25 per cent of the total. It seemed likely that all of the drug was absorbed (or destroyed) before it reached the jejunum. No thiouracil was excreted in the stools. Following a single oral dose of the drug, the highest blood level was obtained within 15 minutes, and urinary excretion began in 30 minutes with the maximal output during the second hour. Blood levels reached a low figure by the end of eight hours and the drug could not be detected after the third day. Urinary excretion behaved similarly with only very small amounts of the drug appearing in the urine after the first day. The average fasting blood level of thiouracil in patients who received daily dosages varying from 0.2 to 1.2 grams was around 2.5 mg. per 100 cc. The cells carried several times (2 to 7) the material obtained from the plasma, the average amount per cell being greater for the leucocyte than for the erythrocyte. A constant blood level was attained by the end of the first day of treatment. Urinary excretion was stabilized shortly thereafter. Total urinary excretion amounted to about one-third that ingested. Blood levels fell rapidly following discontinuance of thiouracil, but the actual time taken for these to reach zero varied from 2 to 5 days in the several subjects studied. Five to seven days was necessary to clear the urine of the drug in those patients who had received it for more than three consecutive days. The amount of fluid ingested was an important factor in the rapidity of excretion. There was less thiouracil in cerebrospinal, pericardial and edema fluids than that found in the blood. Pleural and ascitic fluids showed approximately the same concentration as the blood and that for milk was three times as great. The distribution of thiouracil in the tissues was studied in ten patients dying from a wide variety of diseases and receiving the drug in daily doses ranging from 0.4 to 1.2 grams for periods varying from 2 to 22 days prior to death. The amount stored and the organs in which concentrations were greatest varied materially with the length of time thiouracil had been administered prior to death. In all cases for which the drug had been used more than five days, the tissue concentration was many times that of the blood, in some instances reaching a multiple of 50. In patients dying within three days after the first dose of thiouracil, the greatest concentration of the drug was observed in the pituitary, adrenals, bone marrow and thyroid, respectively. In those dying later, the highest concentrations occurred somewhat in the following order; bone marrow, thyroid, ovaries and pituitary. The adrenals, kidney, spleen and pancreas also contained a large amount, while the testes, liver and muscle concentrated much more poorly. Slices of kidney, pituitary, thyroid, adrenal, pancreas and striated muscle were all active in destroying the drug, with the pituitary most active per unit of weight, and the thyroid and adrenal next. In patients operated for nodular goitres, the concentration of thiouracil in the adenomatous areas was several times that of the rest of the gland.—*T.H.McG.*

WILLIAMS, R. H., A. R. WEINGLASS AND G. A. KAY

Thiouracil storage in the thyroid as affected by thyrotropic hormone and potassium iodide. *Am. J. Med. Sci.* 207: 701. 1944.

The authors administered thiouracil (and in one series of animals potassium iodide as well) in the drinking water simultaneously with thyrotropic hormone subcutaneously to guinea pigs for various periods of time, then sacrificed them and determined the thyroid size and the thiouracil content. They found that thyrotropic hormone given with thiouracil is much more goitrogenic in guinea pigs than is thiouracil alone. Thyrotropin tends to decrease the amount of thiouracil stored in the thyroid while potassium iodide greatly increases the storage of this substance.—*E.C.R., Jr.*

WOLF, A.

The effective use of thyroid in periodic paralysis. *New York State J. Med.* 43: 1951. 1943.

The cases are reported of five subjects of familial periodic paralysis—all related—who responded favorably to thyroid treatment. Failure of thiamine chloride and potassium chloride to afford relief is also reported. An elaborate theoretical discussion of possible endocrine relationships in the disorder is included.—*R.G.H.*